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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

MARCH 1942

THROMBO-ANGIITIS OBLITERANS*

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ALTHOUGH the condition which is now recognized as thrombo-angiitis obliterans probably has been known for many years, the first report on the subject was not made until 1879 by Von Winiwarter. He used the term "endarteritis and endophlebitis" in describing the condition of a man fifty-seven years old who had obliterative arterial disease of the extremities, the symptoms of which had been present for twelve years. After 1879 some isolated reports appeared, but little progress had been made in the knowledge of this disease until the studies of Buerger, which culminated in his report in 1908. Buerger's[1] orderly analysis of a comparatively large number of cases marked an epoch in the study of the disease. His classic report of a study of the arteries and veins in eleven amputated limbs, and subsequent reports, indicate why the disease is commonly called "Buerger's disease," although I prefer to use the term "thrombo-angiitis obliterans," which Buerger gave to this condition in his first publication. The publication of Buerger's book in 1924[2] marked the beginning of widespread interest in thrombo-angiitis obliterans. Since that time reports concerning this disease have been

* Read before the Graduate Fortnight of The New York Academy of Medicine, October 21, 1941.

frequent and sometimes brilliantly done. A partial list of the important contributors to the study of this disease would include the names of Adson, Duryee, Craig, Barker, Brown, Collens, Hines, Horton, Homans, Herrmann, deTakats, MacGovern, Samuels, Silbert, Wright, Wilensky and several associates of these men as well as others. Although the past has been a pleasing chapter, much remains to be uncovered, and the future must produce even brighter contributions before the book about this disease can be closed.

Etiology

The cause is unknown. The lesions in the vessels are inflammatory, suggesting a bacterial or viral cause for the disease. Buerger,[3, 4] with full consent of the patients concerned, produced phlebitis in persons who had thrombo-angiitis obliterans, but whose symptoms at the time were quiescent, by inoculating them with material obtained from acutely inflamed, superficial veins of patients suffering from thrombo-angiitis obliterans. Rabinowitz[5] found a gram-negative organism in the blood of patients who had thrombo-angiitis obliterans, and believed he produced vascular lesions in rabbits with this organism. These results were not confirmed by Jablons.[6] Horton and Dorsey[7] cultured material taken from acutely inflamed veins and arteries obtained at biopsy or at amputation in thirty-four cases of thrombo-angiitis obliterans. Gram-positive pleomorphic streptococci were obtained in pure culture in nine cases, and green-producing streptococci in two cases. Unfortunately, culture of material taken from arteries and veins of amputated extremities of patients who had arteriosclerosis likewise yielded similar organisms, so that the formation of definite conclusions in this study was precluded. Pleomorphic streptococci injected intravenously into thirteen rabbits caused intimal proliferation with thrombosis in two instances. Pleomorphic streptococci were injected into the femoral muscles adjacent to the femoral vessels of forty-two rabbits; intimal proliferation and thrombosis occurred in ten rabbits. Portions of vessels obtained from patients who had thrombo-angiitis obliterans were embedded in positions adjacent to the femoral vessels of twenty-nine rabbits and one dog. Intimal proliferation and thrombosis occurred in seven rabbits, and in one rabbit trophic changes and dry gangrene developed in the toes of the hind feet. This study suggests strongly that streptococci constitute the fundamental cause of vascular lesions in thrombo-angiitis obliterans.

Important support for the belief that the vascular changes are caused by an organism is found in a report of a surgeon who acquired the disease as the result of having a spicule of bone pierce his finger while he was amputating the toe of a patient who had thrombo-angiitis obliterans.[8] Jews are affected more often than Gentiles, but people of all races and nationalities have the disease. Women acquire the disease infrequently.[9] Our studies[10] at the Mayo Clinic indicate that the blood in the presence of this disease is essentially normal but there is no uniformity of opinion concerning this point. Syphilis, malaria, typhus fever and the ingestion of rye bread have been implicated, but are not considered to be important today. The smoking of tobacco accentuates the disease and further impairs the circulation as the result of tobacco-induced vasoconstriction, but there is no evidence that the use of tobacco is the primary cause of the disease. Many puzzling questions remain unanswered when the etiology of this disease is considered. Why does the disease affect men more often than women? Is some endocrine influence thereby indicated? Credence in this theory is adduced by the failure of the disease to affect males before puberty and in the years of sexual decline. Why are the lesions encountered much more commonly in the extremities than elsewhere, and particularly in the lower extremities? Why are Jews more commonly affected than Gentiles? Doubtless the true solution of the cause of thrombo-angiitis obliterans will answer these questions.

Pathologic Aspects

Gross changes in the vessels when thrombo-angiitis obliterans is present are characterized early by thickening of the walls of vessels and later by occlusion of the walls by soft, red thrombi which are finally converted into firm, yellowish-white tissue through which minute blood channels course. Adventitia and perivascular tissue become indurated and the artery, vein and nerve are bound firmly together. The earliest microscopic changes are the appearance of lymphocytes in the adventitia and thickening of the intima arising from proliferation of its cells. This stage merges imperceptibly into that which is characterized by thrombosis and complete occlusion of the lumens of the vessels. Thrombi are organized by the ingrowth of intimal cells and new vascular channels are formed in the intima and media. In the end stage, there are marked fibrosis of the adventitia in which a few lymphocytes may remain, per-

meation of the intima by new blood channels and sometimes by increased interstitial connective tissue, and occlusion of the lumens by very cellular connective tissue through which numerous small blood channels course.[11]

Special Methods of Investigation

These include oscillometry, arteriography, venography, plethysmography, determinations of temperature of the skin, capillaroscopy, calorimetry, tests of circulation time, tests of claudication time, studies of the oxygen content of the blood and the effects on circulation of anesthesia, as well as other tests. Although each of these special methods of study has added somewhat to the knowledge of thrombo-angiitis obliterans, it is none the less true that in actual clinical practice there is little need for most of them. Their greatest value has been in the securing of knowledge concerning chemical, physiologic and pathologic changes which characterize this disease. Sometimes there is a tendency to rely heavily on special methods of investigation for the diagnosis and acquisition of knowledge concerning progress of the disease. Experienced clinicians, on the other hand, rely almost solely on their knowledge of the symptoms of the disease and the information that can be gained with expert use of the visual and tactile senses. Mechanical methods are poor substitutes for clinical experience.

Complications

In addition to thrombo-angiitis obliterans of the extremities, the cerebral, coronary, renal, mesenteric and other intra-abdominal arteries may be involved. For some unexplained reason, when there are clinical manifestations of involvement of the cerebral arteries such as hemiplegia and hemianopsia or evidence of involvement of the coronary arteries such as angina pectoris or myocardial infarction, the organic changes found in these arteries are only occasionally inflammatory in origin and more commonly are arteriosclerotic in nature. The complications mentioned are serious, and may greatly impair the health or terminate the lives of patients who have thrombo-angiitis obliterans, a condition which ordinarily, at most, necessitates amputation of a limb.[12]

Symptoms

The chief symptoms in thrombo-angiitis obliterans are those resulting

from impairment of the arterial blood supply, since inflammation of arteries and veins, with the exception of what occurs in acute thrombophlebitis and acute arteritis, induces insignificant symptoms. The chief symptoms of impaired arterial circulation are referable to temperature, discoloration, pain and ulceration or gangrene. Coldness of the skin is an invariable accompaniment of impaired arterial circulation, but it should be noted that some persons who do not have thrombo-angiitis obliterans and who have normal arterial circulation also have decreased temperature of the skin. These are the persons in good health who have cold hands and feet. The most characteristic discoloration of the skin in thrombo-angiitis obliterans is the excessive pallor which occurs when the affected extremity is elevated and the excessive cyanotic redness of the skin which is noted on prolonged dependency of the affected extremity. Variable degrees of pallor or cyanosis of the skin as the result of exposure to cold or as the result of emotion are not uncommon. The pain of thrombo-angiitis obliterans may be divided into two types: the so-called exercise pain or intermittent claudication and the "rest pain." Intermittent claudication is a symptom which is pathognomonic of impaired arterial circulation. It is a type of distress which occurs only as a result of exercise and which disappears promptly as a result of rest. Characteristically, it affects the muscles in the calf of the leg. Pain is sharp and shooting and gradually increases in severity until the patient must cease the activity which induces it. Intermittent claudication may affect the ankles, toes, plantar surfaces of the feet, and the forearm, wrist or individual fingers. Pain which is experienced while the patient is at rest may affect the feet or hands, usually the digits, before ulceration or gangrene appears. It is usually of a burning, continuous nature, worse at night, and aggravated by dependency. The pain of ulceration or gangrene often is severe, usually localized to the gangrenous or ulcerated regions, of a stinging, burning quality and associated with hyperesthesia about the lesion. Pain may be remarkably severe and persistent. The pain of sudden arterial occlusion is similar to that observed as a result of arterial embolism. The pain of ischemic neuritis is severe, diffuse, involves large areas and does not correspond to the distribution of peripheral nerves. Paroxysmal exacerbations of excruciating, shooting, pulling, tearing pain occur, extending from one end of the extremity to the other. Paroxysms occur most often at night, and may last for several hours.[13]

Clinical Types of the Condition

Slow progression: This is the most common type of the condition. Coldness of the feet, which usually is the first symptom, is followed by excessive fatigue and claudication involving an area such as a single digit, the arch of the foot, wrist, ankle, calf or forearm and by abnormal pallor when the extremities are elevated and by abnormal redness of the extremities when they are dependent. Gangrenous or trophic ulcers may occur.

Absence of progression: In this type mild symptoms of vascular insufficiency (usually excessive fatigue or the pain of claudication) progress slowly for a time and then remain stationary. Trophic changes are limited to proliferation of the nails and increased thickening of the skin over the weight-bearing areas.

Circulatory compensation: This type may belong originally in either of the two types already described. The pain of trophic changes is mild or relieved by medical measures, or the digits may be amputated successfully. Shallow ulcers do not progress and after six months to a year healing occurs. Gradually, other symptoms largely disappear and leave the patient with extremities which are largely adequate for ordinary needs.

Acute fulminating type: Claudication appears relatively suddenly and progresses rapidly. The pain which occurs during rest is severe before gangrenous changes occur and greatly accentuated afterward. Edema and lymphangitis are present around the gangrenous region and slight fever and leukocytosis may occur. Gangrene progresses rapidly; the pain is unbearable and intractable to all measures. Amputation is necessary.

Extensive gangrene without rest pain: This type of condition is very rarely seen. In such cases the diagnosis must await results of pathologic studies.

Venous involvement only: This type of condition is not unusual. The first sign of vascular disease is recurrent superficial or deep phlebitis, which may be present for many years before symptoms and signs of arterial obliterative disease appear.

Normal pulsations in arteries, which usually are palpable: The clinical syndrome usually is that of acute arterial occlusion in one or more digits followed by color changes suggestive of those of Ray-

naud's disease. Gangrene as a rule follows occlusion. Amputation of the digit is followed by healing due to the normal blood supply proximal to the affected regions. Subsequently, other digits may be affected and the obliterative process may progress to a higher level. Diagnosis is dependent on the age, sex and nationality of the patient, the occurrence of superficial phlebitis, the type of pain, the signs of arterial obliteration in single digits, and the finding of organic changes, which are considered to be characteristic of thrombo-angiitis obliterans, in the arteries.

Vasomotor disturbances simulating Raynaud's disease: Clinical evidence in this type of condition is confusing only if the physician fails to recognize the frequent association (30 per cent) of vasomotor disturbances in organic arterial disease. In such cases vasomotor disturbances of the Raynaud type dominate the clinical picture and the organic nature of the disease may be overlooked. The obliterative process is evidenced by signs and symptoms of impaired arterial blood supply. Superficial phlebitis is common.

Associated arteriosclerosis: In this type of condition the signs and symptoms of thrombo-angiitis obliterans are manifested, but there is roentgenographic evidence of calcification of the arteries of the extremities. The radial arteries usually are sclerosed and the age of the patient is at the upper limits, or more than that of the usual patient who has thrombo-angiitis obliterans. Diagnosis is based on a consideration of the age and race of the patient, the occurrence of superficial phlebitis, abnormal postural color changes, the inflammatory zone around the gangrenous ulcer and excessive pain. In many cases microscopic examination of the arteries is necessary before diagnosis can be established.

Severe rest pain without trophic changes: This type is rare. The chief symptom is pain when the patient is at rest, and this pain may equal that which occurs in cases of marked gangrene. The pain is severe, aching or burning and intractable to the usual measures. Examination of the extremities discloses nothing except postural color changes, arterial obliteration and diminished warmth.

Sudden arterial occlusion: Sudden arterial occlusion in thrombo-angiitis obliterans may occur in the course of established thrombo-angiitis obliterans or as the primary manifestation of the disease. The symptoms are similar to those noted in the conventional type of sudden arterial occlusion; namely, a sudden or gradual onset of pain, pallor and coldness or numbness in the extremities.[14]

Physical Observations

1. Pulsation in the peripheral arteries: The most important sign of thrombo-angiitis obliterans is the absence or the impairment of pulsations in usually palpable arteries; namely, the dorsalis pedis, posterior tibial, popliteal, femoral, radial, ulnar, and brachial arteries. It should be kept in mind, however, that thrombo-angiitis obliterans may affect the arteries distal to the point at which pulsations ordinarily can be palpated, although this situation occurs infrequently.[15, 16] There is much to be desired in the matter of general information about determination of pulsations in the peripheral arteries. A comparable situation in auscultation of the heart, for instance, would indicate a chaotic state in the physical diagnosis of cardiac disease. The physician who is interested in the peripheral circulation should, by practice, acquire expertness in the palpation of peripheral arteries.

2. Postural color changes: Abnormal changes in the color of the skin accompanying changes in posture indicate occlusive arterial disease and occur in no other condition. To determine what constitutes normal in the matter of the effect of posture on the color of the skin, the physician should study the color of the skin of his own digits. It is a simple matter to elevate one hand over the head for a few seconds and then quickly move it to the level of the waist, alongside the other hand. It is also simple to lie on a bed when preparing to retire and to determine the effect of posture on the color of the skin of the toes by elevating one leg. When the upper extremities of the patient who has thrombo-angiitis obliterans are being examined, he or she should hold the hands above the head and clench them rapidly five or six times; they are then held open for examination. The person who has normal arterial circulation exhibits slight blanching of the skin as a result of this procedure. If there is significant impairment of the arterial circulation, the skin of the palm of the hand and of the fingers becomes blanched excessively. Frequently, it is observed that the skin of one finger or more is decidedly blanched, whereas that of others appears to be normal; also, the pallor may be distributed in an irregular or patchy form. Although blanching of some extent of the color of the skin of the hands occurs normally when they are elevated above the head, the color returns in a regular manner within five seconds after the hands are in the dependent position. If there is prolongation of the time in which normal color returns to the

skin, impaired arterial circulation exists. When a study of the postural color changes in the lower extremities is made, the patient lies in a face-up position, with his legs flexed at the hips at about a 90 degree angle, in relation to his trunk. The patient may support his extremities by locking his fingers behind his knees. The examiner presses blood from the skin of the elevated extremities by repeated firm stroking of the plantar surface of the foot and toes or he asks the patient to alternately flex or extend the toes or to extend and flex the foot at the ankle for about thirty seconds. Normal persons will exhibit only mild pallor, but when there is marked impairment of the arterial circulation, pallor is extensive and marked. After observation of the color of the skin, the person's feet are turned to a dependent position by having the patient sit with his feet over the edge of the bed or examining table. Usually, normal color returns to the skin of the extremities in about ten seconds. If impairment of the arterial circulation of the extremities is marked, color may return slowly during a period of forty-five to sixty seconds or more. Sometimes it returns in an irregular or patchy manner. Less marked delay of the return of color indicates less marked impairment of the circulation. Excessive rubor of the skin when the extremity is in the dependent position also is a manifestation of impaired arterial circulation, but does not specifically indicate impaired arterial circulation. If cyanotic redness of the skin is more marked than it is among normal persons, it constitutes presumptive evidence of impaired arterial circulation. It is usually limited to parts distal to the wrists and to the ankles, but occasionally it extends for a few inches above the ankle.

3. *Temperature of the skin:* It is well to remember that coldness of the skin does not in itself indicate impaired circulation. However, difference in the temperature of the skin of two symmetric parts is important. Thus, if the digits of one extremity are found to be colder or warmer than the digits of the companion extremity, the probability is great that there is a disturbance of the circulation. The same observation is true when a difference of temperature of the skin is encountered among the digits of the same extremity.

4. *Venous filling time:* After elevation of the extremities until the veins on the dorsum of the foot and the dorsum of the hand have collapsed, the extremities are quickly moved to the dependent position. Among normal persons, there is evidence of filling of the veins on the dorsa of the feet and hands within ten seconds. Whenever more than

ten seconds is required for these veins to show evidence of filling, impairment of arterial circulation should be suspected.[17]

5. Phlebitis: This manifestation usually affects the superficial veins in thrombo-angiitis obliterans, but occasionally the deep veins may be involved. Superficial phlebitis is characterized by red, tender zones along the course of veins and the presence of a palpable thrombus in these veins. After the acute phase of thrombophlebitis subsides, there may be characteristic staining of the skin with blood pigment, which will persist for long periods. Deep thrombophlebitis does not differ from that observed in other conditions.

6. Gangrene and ulceration: These conditions are almost always limited to the distal parts; that is, the ends of the fingers and toes. Gangrene may extend, however, to involve almost the entire foot or the entire finger. When localized gangrenous or ulcerating lesions affect more proximal parts of the hand or foot than the digits, the probabilities that these lesions have been induced by various kinds of trauma are great.

Diagnosis

Thrombo-angiitis obliterans should be suspected whenever unexplained gangrene affects the extremities, whenever intermittent claudication occurs, whenever superficial phlebitis recurs and whenever the extremities are cold, discolored or affected by episodes of discoloration. The diagnosis of chronic occlusive arterial disease is based on the finding of diminution or absence of pulsations in the dorsalis pedis, posterior tibial, popliteal, femoral, radial or ulnar arteries. Confirmatory signs are abnormal coldness of the extremities, excessive pallor when the extremities have been elevated for a few minutes, slow return of color and delayed filling of veins when the extremities are put in the dependent position after elevation, and abnormal redness or cyanosis when they have been in the dependent position for a few minutes.

The only condition which offers any great difficulty in differential diagnosis is arteriosclerosis obliterans, which is also a chronic occlusive arterial disease (Table 1).

Treatment

Intelligent treatment of thrombo-angiitis obliterans necessitates full consideration of the following conditions.

Thrombo-angiitis obliterans is a self-limited disease. The chief aims

TABLE 1

DIFFERENTIAL DIAGNOSIS OF CHRONIC OCCLUSIVE ARTERIAL DISEASE AFFECTING THE EXTREMITIES*

Diagnostic points	Thrombo-angiitis obliterans	Arteriosclerosis obliterans
Age	Between 25 and 45 years	Between 55 and 85 years
Sex	Males, 99%	Males, 90%
Race	Jewish, 42%	Any
Pulsation of arteries	Pulseless, 50% Diminished, 45% Normal, 5%	Pulseless, 50% Diminished, 45% Normal, 5%
Claudication	Usually present	Usually present
Excessive rubor with dependency	Present	Present
Excessive pallor with elevation	Present	Present
Gangrene	Common	Common
Rest pain	Usually very severe	Usually mild
Type of rest pain	Sharp, stinging	Aching
Appearance of gangrenous ulcers	Moist, inflamed, discharging	Usually dry
Superficial phlebitis	30% of cases	Absent
Roentgenogram of arteries	Usually negative for sclerosis	Usually positive for sclerosis
Color changes after exposure to cold	30%	15 to 20%
Temperature of extremities	Low	Low
Edema	Frequent	Infrequent
Fats in the blood	Normal	Frequently increased

*In a table such as this, only the usual situation can be outlined; there are exceptions; percentages are approximate.

of treatment are two: (1) prevention of progression of the disease and (2) establishment of collateral circulation which will be sufficient to maintain life in the peripheral tissues in spite of occlusion of the chief arteries. Occasionally, a physician feels that it is wiser to amputate the lower extremities than to carry out conservative treatment for a long period. Such an attitude neglects two observations: first, amputation can be prevented in the vast majority of instances if adequate medical treatment is carried out; and second, amputation of the extremities does not eradicate the disease, which may continue to progress in other regions, namely, the heart, brain and the intra-abdominal regions. Ade-

quate clinical observation by a number of careful students of the disease has indicated that without doubt much can be accomplished in the medical treatment of thrombo-angiitis obliterans and that under good supervision the incidence of amputation is remarkably low and disability surprisingly slight. These statements do not express satisfaction with the present methods of treatment, for there is much room for improvement. This attitude does, however, take exception to that held by many physicians: that nothing can be done for the patient who has thrombo-angiitis obliterans.

In a consideration of the correct treatment of a patient who has thrombo-angiitis obliterans with gangrenous lesions, ulcers or pain while the limb is at rest, both patient and physician must be thoroughly imbued with the idea that treatment for a comparatively long period is essential if the best results are to be attained. It is sometimes well to point out to a patient that many diseases, such as tuberculosis, for example, require treatment for months, and that thrombo-angiitis may be as demanding of time as the aforementioned disease. If this situation is discussed with the patient suffering from thrombo-angiitis obliterans soon after treatment is begun, he is easily reconciled to slow progress, a state of mind which in itself seems to hasten improvement. It is impossible to state precisely when medical treatment should be abandoned for amputation if amputation is necessary, since the criteria for amputation vary greatly from case to case. In general, in cases in which severe pain cannot be controlled adequately by medical or neurosurgical means or in which gangrenous lesions do not respond to intensive medical treatment for a considerable period, amputation is required. The physician who encounters many patients suffering from thrombo-angiitis obliterans actually encounters three types of conditions, in two of which decision as to treatment is not difficult. In the first prompt amputation is advisable, and in the second amputation need not be considered. For patients who have the latter condition medical treatment and sympathectomy are clearly indicated. In the third condition, however, the question arises at once as to whether or not amputation is advisable. In such circumstances it is best to treat patients conservatively for a minimal period of several weeks. If unsatisfactory progress results from this regime, amputation may be considered. If the treatment causes improvement, it may be continued.

The physician may object at once that thrombo-angiitis obliterans

is a chronic disease and that healing of lesions such as those described does not necessarily mean that cessation of the disease has occurred. He may point out that amputation may be advisable eventually and that there is little reason for deferring the time when such treatment is necessary. Such an attitude prompts the decision to amputate limbs as soon as the diagnosis of thrombo-angiitis obliterans is made. Fortunately, the poor logic of this is apparent, for many patients suffering from thrombo-angiitis obliterans have two fairly normally functioning legs all their lives and many others may be spared one normally functioning leg.

Other physicians may point out that the cost of conservative treatment for a long period is great. It is almost always a good policy to discuss the situation frankly with the patient. If he desires a trial of conservative treatment it seems to me he should have it. If such treatment impresses him as being too costly and too uncertain of producing good results, amputation may be advisable. Too many factors influence the patient to allow the physician to advise him dogmatically. The physician should not allow a poorly founded attitude of pessimism on his part to influence the patient to accept amputation when it may not be necessary. Some patients are treated conservatively too long, but in many instances "too poor" treatment is mistaken for "too long" treatment. I cannot agree that the cost of an intensive but conservative program for a few weeks is too great, if there is a chance of producing healing of gangrenous lesions and quiescence of the disease. I believe that the incidence of amputation for thrombo-angiitis obliterans has been sharply reduced and that it can be further reduced. Earlier recognition, better conservative treatment and less of an impetus toward amputation in many cases are very desirable.

Abstinence from tobacco: The use of tobacco in any form should be denied every patient who has thrombo-angiitis obliterans. It is apparent that it is largely useless to treat patients who continue to use tobacco.

Protection of the extremities: It is important that the extremity or extremities be cared for properly if gangrene is to be prevented. In more than 50 per cent of cases, gangrene is precipitated by some avoidable injury. The patient should do all he can to avoid crushing or bruising of the feet or toes and to avoid scratches, cuts, fissures in the skin, burns, blisters and frostbite. Only comfortable shoes which do not bind or rub should be worn, and the patient should "break in" new shoes

gradually by wearing them about an hour daily. Felt shoes or sheepskin shoes should be worn in cold weather if the patient is subjected to cold. Diminished activity on the feet is advisable. Patients can carry on ordinary activities, if they are not too strenuous. However, they should attempt to rest the feet as much as possible. In some instances it may be advisable to begin treatment with cessation of all but necessary activities for a month or so. Toenails should be cut straight across after they have been soaked in warm water; corns, calluses and bunions should not be trimmed or incised. Removal of ingrown toenails and minor operations on the toes have caused many instances of gangrene, and these minor surgical procedures should be avoided unless they are performed by a physician who is familiar with the disease. The feet should be washed carefully and gently every day with mild soap and warm water; they should be carefully dried and then 50 per cent alcohol should be applied. If the extremities are excessively dry and the skin tends to crack or scale, they should be rubbed gently with hydrous lanolin or cocoa butter once or twice a day. Preparations containing iodine, merthiolate, sulfonaphthol, carbolic acid, cresol and lysol should be avoided because they may cause ulceration or gangrene. Trichophytosis should be actively treated—but not in the usual manner, because preparations containing salicylic acid may cause ulceration. A safe method of treatment is to soak the feet for half an hour twice daily in a 1:8000 solution of potassium permanganate.

Measures designed to increase the circulation: It may be determined by a reading of the literature that there is a wide divergence between the evidence derived from physiologic studies which indicates improved circulation, on one hand, and the clinical manifestations accepted by various authors as constituting evidence that there was improvement in circulation, on the other hand. This situation has been brought about largely because of the failure of physicians to understand that many diseases are subject to marked remission and accentuation in their natural courses. It is brought about also by the fact that those physicians who are relatively inexperienced, in that they have seen but few instances of impaired circulation, do not have the background which would enable them to interpret clearly the effects of various measures. Finally, confusion is brought about because some authors have advocated vigorously and enthusiastically their own particular methods of treatment when there has been inadequate physiologic foundation for such en-

thusiasm. One need not have been long interested in disturbances of the peripheral circulation to notice that some measures accepted enthusiastically by the medical profession at one time are now largely disappearing from the scene. There is no quality of unkindness in these remarks, for as long as physicians are human beings, enthusiasms will wax and wane and methods will come and go. It does seem advisable, however, for me to make a plea for physiologic evidence that methods which are advocated in the treatment of circulatory disturbances have a beneficial effect upon the circulation. Yet, even physiologic evidence that circulation is improved *temporarily* by specific methods cannot recommend the particular method in question too highly. The best method of treatment would be one which could be shown by the results of physiologic studies to produce permanent improvement of the circulation. Instrumental method A may be shown to improve the circulation temporarily, but it has no virtues over simpler methods of treatment (for example, an environmental temperature of 86° F. [30° C.] which also increases circulation) unless it produces a permanent increase in the circulation. As clinicians, therefore, we are most enthusiastic about a method of treatment which produces a permanent increase in the circulation as shown by physiologic studies, less enthusiastic about methods which produce temporary improvement in the circulation as shown by physiologic studies, and least enthusiastic about methods of treatment which cannot be supported by physiologic studies but which clinically seem to have value. It is well to emphasize herein that data concerning the beneficial results of some particular method of treatment which are based on observation for a long period are of little value, because, as has been noted, there is a distinct tendency for disturbances of the peripheral circulation to regress and progress, and because it is almost always true that no single method of treatment of this disease is carried out. Each physician instructs the patient in the care of his extremities, insists on cessation of smoking, in many instances puts the patient to bed, improves his nutrition and relieves his pain. To this basic groundwork of treatment Doctor A adds method A, Doctor B adds method B, Doctor C adds method C and so forth. Unfortunately, in reporting his results, Doctor A is likely to attribute all improvement to method A, whereas Doctor B is likely to attribute all improvement to method B, and Doctor C is likely to attribute all improvement to method C. This seems to me to be the only explanation for the astonishing correlation of good

results reported from a number of different methods of treatment. Study of the literature reveals that almost all methods of treatment produced good results in a large percentage of cases. This raises the suspicion that it was not the specific treatment alone which produced improvement, but the basic framework of treatment in addition to the specific method of treatment. The most optimistic notes in any consideration of diseases of the peripheral circulation are the great strides that have been made in the progress of therapeutics. These, it seems to me, are more important than the determination of the specific reason for therapeutic improvement.

Local application of heat to the extremities: This may be advisable and may be administered in the form of radiant heat from a carbon filament bulb placed in a cradle or baker. The temperature about the feet should not exceed 100° F. (37.7° C.). Exposure of the extremities to this warmth for an hour two or three times a day is advisable.

Warm sitz baths: These also improve the circulation temporarily.

Postural exercises: These may be helpful, although there is, so far as I know, no evidence that they produce improvement in the arterial circulation. Patients should elevate the extremities for one minute, then place them in the dependent position until rubor becomes maximal, then lie with them in a horizontal position for one minute. These procedures should be repeated five times, two or three times each day.

Contrast baths: These may be advisable. There should be two containers, each large enough to permit immersion of both feet to the midportions of the legs. In one container is placed cold water (40 to 50° F. or 4.4 to 10° C.) and in the other, warm water (102 to 105° F. or 38.8 to 40.5° C.). The feet are alternately immersed in each container for one minute for a period of about fifteen minutes, two or three times a day. I know of no evidence that this procedure improves the arterial circulation.

Intermittent suction and pressure (pavex) treatment: In some instances this should be carried out for two or three hours daily.[18,19] The pressure should be varied, depending on the comfort which the treatment affords and the effects on circulation, but generally a positive pressure of 40 mm. of mercury and a negative pressure of 80 to 100 mm. of mercury are advisable. Ordinarily, a complete cycle should occupy about fifteen seconds. Disappearance of symptoms, healing of ulcers and objective evidence of improved arterial circulation have been reported

to result from this method of treatment. As these reports and others are studied, the reader is impressed with the fact that the physiologic evidence of improved blood flow as the result of this method of treatment is based on a few determinations of the temperature of the skin and on the observation that the flow of liquid through a mechanical schema could be increased by this method of treatment. Cautious question of whether the results on the circulation thus achieved are only temporary seems well founded. Physicians vary greatly in their evaluation of this method of treatment, some are enthusiastic, others believe the method has no virtue. Certainly it is true that in most instances the enthusiasm displayed when the technique first became available has waned, but there still seems to be a place for this method. This type of treatment, as well as intermittent venous compression and passive postural exercises as made possible on the Sanders bed, should be carried out in a room, the environmental temperature of which is about 90° F. (32.2° C.), or in conjunction with the local application of radiant heat.

Intermittent venous obstruction: This technique is considered advisable by some physicians.[20,21] In developing this method of treatment, Collens and Wilensky utilized the observation of Lewis and Grant,[22] who found that an increase in arterial amplitude occurs during venous congestion and that an increase in the arterial flow much out of proportion to the original resting rate occurs when venous congestion is relieved. Evidence is largely or entirely lacking that this reactionary hyperemia does more than repay the debt in circulation which occurs during the period of venous occlusion. Even students of the physiology of the circulation do not agree as to whether or not this method of treatment improves the peripheral circulation. For example, Abramson and associates,[23] who studied circulation with a plethysmograph, found that "In no instance was a sustained increase in blood flow observed in the leg or forearm during or following this procedure." Linton and his associates,[24] however, concluded on the basis of results of an experimental study that during the period of venous compression a rather marked increase in arterial inflow occurs. Results of recent studies not yet reported cast grave doubt on the validity of previous observations that intermittent venous occlusion causes an improvement in arterial circulation. It is possible, however, that this method of treatment produces good results in some manner other than by improvement of the arterial circulation. The situation is similar to that which obtains in intermittent

suction and pressure, as far as clinicians are concerned. Some are enthusiastic, others feel that the method has no virtue. Although machines are available which will perform this function automatically, it can be carried out by placing the cuff of a sphygmomanometer about the patient's thigh or arm. The cuff is inflated to a pressure of about 80 mm. of mercury for from two to nine minutes and then deflated for about two minutes. This treatment should be carried out for a minimum of about four or five hours daily.

The Sanders bed: The Sanders bed in brief consists of an ordinary hospitable bed attached to a special cradle so that the bed can be rocked on a transverse axis across its midportion after the manner of a child's see-saw. By means of an electric motor, the bed is tipped on this transverse axis continually, so that the head of the bed is alternately raised and lowered to an arc of approximately 60 degrees. The period of oscillation can be adjusted, so that a complete cycle can be completed within any interval from one to seven minutes. The use of the bed makes use of the old principle of postural exercises described previously.[25] Barker and Roth[26] noted that by means of this bed pain associated with ulceration and gangrene, pain caused by ischemic neuritis and pain which occurred in the digits without ischemic neuritis or gangrene, was relieved. They thought that in comparison with other mechanical means of treatment of peripheral circulatory diseases, the Sanders bed possesses the advantage of ease of use. As far as I know there is no conclusive physiologic evidence that this mechanical method of treatment improves peripheral circulation, but the clinical results obtained with this type of treatment are occasionally striking.

Hypertonic solutions of sodium chloride: The injection of hypertonic solutions of sodium chloride may aid.[27,28] In cases of thromboangiitis obliterans without gangrene from 250 to 350 cc. of a 3 to 5 per cent solution are injected, twice or three times a week for about three months; then the frequency of injection is gradually diminished for about six months. In cases of gangrene injection is done three times each week until healing occurs, or until the hopelessness of further treatment has been established. The solution should be injected through a 19 gauge needle at the rate of about 30 cc. per minute. Much controversy exists concerning the efficacy of this method of treatment. Samuels and Silbert obtained excellent clinical results with it; others have believed that the solution of sodium chloride is of little or no benefit. My own doubt and

that of others concerning this method of treatment is based on the conviction that the original premise on which this treatment rests is false; namely, that there is an increased viscosity of the blood in thrombo-angiitis obliterans which can be corrected by the injection of hypertonic solutions of sodium chloride. There is some objective evidence that circulation in the peripheral arteries increases as a result of this method of treatment,[29] but Abramson[23] concluded as a result of plethysmographic studies that only occasionally did the intravenous injection of hypertonic solutions of sodium chloride improve the peripheral circulation.

Typhoid vaccine: Certainly one of the best methods of increasing the circulation in thrombo-angiitis obliterans is the repeated induction of fever by means of the intravenous injection of typhoid vaccine.[30] At the Mayo Clinic we use a vaccine* which contains killed typhoid, paratyphoid A and paratyphoid B organisms. The desired reaction is elevation of the oral temperature to from 101 to 102° F. (38.3 to 38.8° C.). Chill, headache and malaise may result. Excessive elevation of the oral temperature, severe chills, and marked malaise are not necessary and are to be avoided if possible. The quantity of vaccine originally injected contains 15,000,000 to 25,000,000 bacteria for a man and about half this amount for a woman. Ordinarily, each subsequent dose is increased by from 15,000,000 to 25,000,000 bacteria, but the amount injected depends on the reaction. If the reaction to any injection is too severe, the amount subsequently injected should be increased only slightly or not at all. If the reaction is too mild, the quantity next injected should contain 25,000,000 to 50,000,000 bacteria more than did the quantity previously injected. Injection may be done once or twice a week for six or eight weeks, after which a period of rest of several weeks is advisable before another course is begun. Contraindications to the intravenous injection of typhoid vaccine are advanced debilitating diseases, diseases of the coronary and cerebral arteries, a chronic nephritis, mild cardiac insufficiency, active pleurisy or pericarditis, latent or quiescent appendicitis and cholecystitis.[31] It is our observation, made repeatedly, that the beneficial effects of the intravenous injection of typhoid vaccine persist beyond the period of the fever. Usually, fever which lasts six or seven hours will provide relief of pain for days and it is a rather common clinical observation that lesions characterizing impaired arterial circulation may continue to improve for a period which is much longer than the

*Lederle Laboratories, Inc., New York.

duration of the fever itself. It is my opinion, but one which I cannot develop on the basis of evidence, that the repeated intravenous injection of typhoid vaccine has an ameliorating effect on the course of the thrombo-angiitis obliterans.

Short wave diathermy: This distinctly improves the peripheral circulation, but the effects of such treatment are of short duration.[32] Terminals should not be applied to affected limbs.

Heating sleeve and heating boot: This method promises to be of substantial value in the treatment of thrombo-angiitis obliterans.[33] It is a method of inducing vasodilation in the lower extremities by heating the upper extremities, but it has not yet been perfected from a mechanical standpoint.

Miscellaneous methods: The ingestion of alcohol improves the peripheral circulation and may be used judiciously. Papaverine, theobromine, calcium, parathyroid extract—Collip (para-thor-mone), desiccated thyroid substance, sodium thiosulfate, iodides, prostigmine, estrogenic substances, testosterone propionate, sodium chloride taken orally and other agents or methods of treatment have been said to improve the peripheral circulation in thrombo-angiitis obliterans, but in most instances supportive evidence of these claims is lacking.

Sulfanilamide: It has been my impression that *sulfanilamide* is of value in the treatment of thrombo-angiitis obliterans, particularly of that type which progresses rapidly. If no untoward reactions occur, sulfanilamide may be given in amounts of 60 to 90 grains (4 to 5.8 gm.) daily (enough to keep the concentration of the drug in the blood at 6 to 8 mg. per 100 cc.) for a period of two weeks, which is followed by a rest period of two weeks, at the end of which the treatment can be given again. The alternating method of administration may be continued for two or three months if the patient tolerates the treatment well.

Drugs which impair coagulation of the blood: 1. Heparin.—Heparin might be valuable in the prevention of thrombosis which occludes the arteries and veins in thrombo-angiitis obliterans, but difficulty of administration and the cost are prohibitive.

2. Coumarin compound: This preparation, made from spoiled sweet clover (3,3′ methylene-bis- [4-hydroxycoumarin]), which prolongs coagulation and prothrombin time of the blood, may be useful in the treatment of thrombo-angiitis obliterans, since it impairs coagulation of the blood and may prevent thrombosis. It may be administered orally

for long periods, and is not expensive.[34] Much work remains to be done before any conclusions can be formed concerning the usefulness of this preparation.

Treatment of intermittent claudication: This can be treated by the use of tissue extract. Of these the deproteinated tissue extract* is as good as any.[35] It can be injected into the deltoid muscles in amounts of from 3 to 5 cc. If a daily injection for four or five days greatly increases the distances which the patient can walk before the pain of claudication occurs, the injections can be diminished gradually in frequency until a plan is developed which produces maximal therapeutic results. So far as I know, this treatment does not improve circulation, but is intended only to increase the distance the patient can walk before pain occurs.

Treatment of severe pain which occurs while the patient is at rest: Severe pain may affect the extremities when the patient is at rest, when trophic changes are present or when the skin is unbroken.[36] In many instances morphine sulfate or dilaudid must be used, but the habituation to these drugs should be avoided. Codeine sulfate is efficacious in many instances. The artificial induction of fever by means of the intravenous injection of typhoid vaccine may produce marked relief. Other measures, such as intermittent suction and pressure, intermittent venous obstruction and the intravenous injection of solutions of sodium chloride, should be tried. When pain does not respond favorably to these measures and the patient loses morale and weight and is unable to sleep, section or crushing of, or the injection of alcohol into, the posterial tibial, peroneal and sural nerves may produce anesthetization of the skin and relieve pain.[37] In other instances it is advisable to inject alcohol into the spinal canal for the purpose of affecting the posterior nerve roots.[38] Neither of these procedures should be carried out by anyone other than an experienced surgeon. Amputation may be necessary.

Local treatment of gangrene: The wound should be kept clean and the extremity should be soaked for from two to four hours daily in a warm saturated solution of boric acid or a 1:8000 solution of potassium permanganate or an 0.5 per cent solution of chloramine. In some instances surgical cleansing may be advisable, but this should be performed only by an experienced surgeon. It is only rarely that a toe can be successfully amputated, for the incision necessary to this procedure ordinarily does not heal. Contrary to this situation, if fingers are amputated

*Depropanex, Sharpe and Dohme.

the wounds almost invariably heal. In all cases of trophic changes involving the digits patience must be exercised, for it is often necessary to treat patients actively for weeks or months before the grangrenous part sloughs and granulation and epithelization occur. Other measures, such as those mentioned in the preceding paragraphs, should be used. When the ulceration is free from infection and the base is covered with granulation tissue, some of the epithelial stimulants, such as thioglycerol, promote healing. When evidence of infection is present, sulfanilamide may help. When massive gangrene affects an entire foot, amputation ordinarily is the best procedure. In about 80 per cent of the cases healing follows amputation of the extremity below the knee, but it is occasionally necessary to perform reamputation above the knee. The necessity for amputation of the forearm has never been observed.

Treatment of recurrent superficial phlebitis: There is no known method for the successful prevention of recurrence of superficial phlebitis in all instances. In some cases removal of foci of infection may be of value. Acute episodes are best treated by rest in bed and the application of moist, warm packs in which a saturated solution of magnesium sulfate or boric acid is embodied. In some instances roentgen irradiation of the inflamed veins may speed resolution. Sulfanilamide may help.

Value of sympathectomy:[39] Removal of the sympathetic nerve supply to the extremity is performed for the single purpose of increasing the flow of blood. This procedure does not ordinarily affect intermittent claudication, or prevent recurrence of superficial phlebitis or progression of the disease. It does, however, increase the blood supply to nearly maximum and minimizes the danger that gangrene will necessitate amputation. It should be carried out only when trophic lesions are minimal and healing, or when they are entirely absent and when pain which occurs during rest has been almost entirely relieved or is entirely absent. Whether or not the blood supply can be significantly increased by sympathectomy may be determined by thermometric study of the extremity after the artificial induction of fever by the intravenous injection of typhoid vaccine. Thermocouples are applied to two or three digits of each extremity, one of which is the most extensively involved. Fever is induced by the intravenous injection of a suitable amount of typhoid vaccine. If the increase in the temperature of the skin is markedly in excess of the increase in the oral temperature, or if the maximal cutaneous temperature less the increase in the oral temperature exceeds an

approximate value of 32° C. (89.6° F.) sympathectomy will significantly increase the circulation. Naturally, the kind of treatment to be employed will depend on the clinical syndrome as indicated in the following rough outline:

1. Intermittent claudication and cold, discolored extremities.
    a. Cessation of use of tobacco
    b. Prophylactic care
    c. Tissue extracts
    d. Sulfanilamide
    e. Occasional injection of typhoid vaccine
    f. Sanders bed, pavex or intermittent venous occlusion for two hours daily, or repeated injection of hypertonic salt solutions
    g. Sympathectomy in place of "e" and "f"
2. Limited ulceration or gangrene with rest pain
    a. Cessation of use of tobacco
    b. Hospital care in an environmental temperature of about 90° F. (32.2° C.)
    c. Sulfanilamide
    d. Local care of gangrene or ulceration
    e. Typhoid vaccine
    f. Use for several hours daily of Sanders bed, pavex or intermittent venous occlusion
    g. Hypertonic salt solutions
    h. Section of peripheral nerves if necessary for relief of pain
3. Extensive gangrene or limited lesions which do not heal as a result of weeks of treatment
    a. Amputation

Summary

Thrombo-angiitis obliterans is a disease of unknown etiology which is characterized by inflammation of veins and arteries, chiefly in the extremities, leading to thrombosis of these veins. The disease produces its detrimental effects chiefly by means of impairment of the arterial circulation. A well-planned program of treatment in which physician, orthopedist and neurosurgeon should participate frequently results in cessa-

tion of the disease and preservation of the extremities. Although many questions concerning this disease remain unanswered and although treatment is by no means entirely satisfactory, great strides have been made in the past decade and a half in an understanding of the disease and in methods of treatment.

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EFFECTS OF RENAL EXTRACT ON HYPERTENSION*

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At the present time there are two widely accepted concepts of the pathogenesis of hypertension. According to one of these, which we may designate as the monogenetic theory and which was advocated by Bright[1] and his early followers, the increased peripheral resistance is primarily dependent on renal disease. This concept, once widely accepted, was challenged during the latter part of the last century by numerous writers, including Mahomed,[2] Huchard[3] and Allbutt.[4] The evidence for their contention was as follows: (a) Hypertension often exists in the absence of clinical evidence of renal disease; (b) Postmortem examination of the kidneys of hypertensive persons frequently reveals only minimal evidence of renal disease; (c) hypertension may develop in the course of certain diseases of the endocrine glands or of the nervous system without evidence of any primary renal disorder. (The increase in blood pressure which sometimes sets in with diphtheritic paralysis and disappears with recovery constitutes a rare but pertinent example.)

The evidence against the monogenetic (renal) theory therefore seemed conclusive and an alternative concept developed. According to this, the polygenetic theory, hypertension was of at least two types: renal; and "essential"—this latter term implying non-renal, cause unknown.

In recent years, attempts have been made to subdivide essential hypertension into a large number of different types.[5, 6, 7] Such a separation, insofar as it has been successful, has tended to cast further doubt on the validity of Bright's monogenetic (renal) hypothesis. Anyone who bases his conclusion on the available clinical evidence alone must necessarily adopt the polygenetic theory. Such a point of view is, however, much too narrow. It is necessary that we survey all the evidence—experimental as well as clinical. Although temporary hypertension has

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been caused in an occasional animal for many years, it is only within the past decade that it has been possible to induce with consistency a condition resembling chronic hypertension in man. The procedure of subtotal nephrectomy, employed successfully in rats by Chanutin and Ferris[8] in 1932, did not immediately lead to rapid advances because there was no satisfactory method for repeated measurement of the blood pressure of such small animals. This difficulty has now been overcome.[9] However, it was the now classical work of Goldblatt and his co-workers,[10] begun in 1928 and published in 1934, which offered for the first time a readily reproducible and feasible method of producing chronic hypertension in the dog, and which indicated the importance of disease of the renal blood vessels as a cause of hypertension. For technical reasons the method of subtotal nephrectomy has not been successful in dogs and the induction of renal ischemia has yielded unsatisfactory results in rats. Hence, the procedure of Page,[11] wrapping the kidney in silk and production of perinephritis, which yields chronic hypertension in both species, has been of great practical value.

As the result of these newer studies, and more particularly because of the work of Goldblatt, attention has again been focused on the role of the kidney, and the polygenetic theory with its concept of "essential" (non-renal) hypertension has been seriously challenged. Goldblatt showed that under certain conditions dogs with renal hypertension may present clinical and pathological findings analogous to those found in patients with the so-called essential hypertension. Thus, the very foundation stones of the polygenetic theory were shaken. However, the existence of hypertension clearly related to certain disorders of the nervous system and of the endocrine glands remains to be explained.

Another important result of Goldblatt's work was the demonstration that renal hypertension is independent of renal excretory failure; the evidence being that renal hypertension could exist in the presence of normal chemical composition of the blood. Our own subsequent observations confirmed this conclusion for we were able to show in dogs that bilateral ureteral ligation caused hypertension, while bilateral nephrectomy did not. This conclusion, i.e., that renal hypertension is the result, not of retention products, but of the presence in the body of malfunctioning renal tissue was the starting point of all our subsequent studies.

The Renal Pressor Mechanism

Denervation experiments seem to have demonstrated clearly that experimental renal hypertension is not of reflex origin. In searching the literature for a clue as to some possible chemical factor we found that Tigerstedt and Bergmann[12] had described in 1898 a pressor substance of renal origin to which they gave the name "renin." This substance had apparently been overlooked by most subsequent investigators but, following the publications of Harrison, Blalock and Mason,[13] and Friedman and Prinzmetal,[14] interest in it was revived. During the past four years numerous studies concerned with this pressor substance have been made. Of these the most significant would seem to be those of the Indianapolis[15, 16] and Buenos Aires[17] groups. Their work indicates that renin interacts with blood serum to form a highly active pressor substance ("angiotonin," "hypertensin") which is thought to be the effective vasoconstrictor agent. Although the view that these renal pressor substances are concerned in renal hypertension forms the basis of a plausible theory in agreement with many known facts, there is also evidence against this view.[18, 19] Regardless of this question, the only point which concerns us here is that studies on the renal pressor substance first led to the concept of a renal anti-pressor mechanism.

The Renal Anti-Pressor Substance

The idea that the normal kidney might produce a substance which would be beneficial when administered to animals or patients with renal disease is not a new one, having been advanced as early as 1892 by Brown-Sequard,[20] and having been revived more recently by Gomez[21] in France and Jablons[22] in this country. Their concepts have not received general acceptance because these authors offered neither rational *indirect* evidence that such a substance *should* exist nor convincing *direct* evidence that such a substance *did* exist.

In the case of our own work the original indirect evidence that a renal anti-pressor substance should exist was rather strong. It may be summarized as follows:

1. Bilateral nephrectomy causes increased sensitivity to renin. The effect is not due, as Tigerstedt and Bergmann suggested, to lack of excretion because *this increased sensitivity develops slowly one or more* days after removal of the kidneys.[23]

2. The blood pressure of hypertensive rats declines during the latter part of pregnancy and rises after delivery. Normal pregnant rats display diminished sensitivity to renin. These effects may conceivably arise from the fetal kidney.[24]

3. Crude (saline) extracts of normal kidneys tend, on standing, to become less pressor; those from ischemic kidneys tend to become more pressor.[25]

4. Crude renal extracts containing renin produce progressively less pressor effect upon repeated injection.

5. Senile rats are more sensitive to renin than young adult rats. One would expect senility to be associated with deficiency rather than excess of incretory substances.

* * *

Although the evidence which has been mentioned suggests rather strongly that normal renal tissue exerts some type of anti-pressor action, it is of indirect nature and hence not entirely convincing. Furthermore, this evidence is, in part, based on the assumption that the renal pressor substance—renin—does in fact play a role in the genesis of renal hypertension. This assumption which is supported by some of our own observations and very strongly supported by the observations of Page, *et alii*, is not regarded as entirely convincing by all the workers in this field, nor even by ourselves. Obviously, therefore, the further assumption of a renal anti-pressor substance could not be accepted on the basis of indirect evidence alone. Fortunately, direct evidence is now available. This was first presented by ourselves[26, 27, 28] and we were gratified when we learned that Page, Helmer, Kohlstaedt, Fouts, Kempf and Corcoran[29, 30] had arrived at similar conclusions, their work having been performed independently and only shortly after ours. The observations have recently been further confirmed by Jensen, Corwin, Tolksdorf, Casey and Bamman.[31] Further evidence along somewhat similar lines has been presented by Braun-Menendez, Fasciolo, Leloir and Munoz,[32] who found that extracts of various tissues caused enzymatic destruction of "hypertensin;" by Schroeder,[33] who reported decline in blood pressure following the injection of tyrosinase; and by Wakerlin and Johnson,[34] who found that the blood pressure of dogs with renal hypertension could be reduced by the administration of renal extracts containing renin.

What, then, is the direct evidence for the existence of a renal anti-

pressor substance? It consists in a demonstration that the blood pressure of animals with renal hypertension may be reduced by the administration of an extract prepared from normal renal tissue. We have obtained this result in approximately one thousand rats and in about a score of dogs. In our first experiments the material was administered by injection but, after having discovered the effectiveness of the extract when given by mouth, we have employed the oral route almost exclusively. It is now generally recognized that a number of non-specific noxious substances derived from animal tissues may exert a depressor action when administered parentally. Probably some of the reductions in blood pressure observed by earlier investigators, using crude extracts of various tissues, are to be ascribed to such an action. None of these extracts of previous authors have been shown to produce decline in blood pressure when administered by mouth. Although oral administration of our renal anti-pressor substance requires much greater quantities of the extract, it renders the results more convincing by reducing the likelihood of obtaining—from impure extracts—declines in blood pressure due to non-specific or toxic substances.

One naturally wishes to know whether the extracts containing the renal anti-pressor substance are of any value in treating patients with hypertension. In May 1939, we reported two patients who had exhibited decline in blood pressure following the administration of such extracts.[26] In June 1940, observations on five patients were presented.[28] Since that time we have treated only four additional patients. (The number is small because of the expense and the technical difficulties involved in preparing the huge quantities of the extract required for human use.) Of these four patients one was in advanced uremic coma and died within a few days after treatment was instituted. The decline in blood pressure which this patient exhibited would probably have occurred as a terminal event in any case and no significance can be attached to it.

A second patient received large amounts of an active extract orally but no decline in blood pressure occurred. Whether this negative result is to be ascribed to destruction in the gastrointestinal tract, to failure of absorption, or to refractoriness of certain types of hypertension to this form of therapy is uncertain.

The third patient was a young man with glomerulonephritis who was carefully studied during several months in the hospital. On two separate occasions a moderate decline in blood pressure associated with

subjective improvement occurred following administration of renal extract. The decline in blood pressure endured for two or three weeks after therapy was withdrawn. The blood pressure then gradually ascended to the original level and again declined when therapy was resumed and rose after the extract was discontinued.

The results in the fourth patient seemed to be remarkable. This young man had a typical picture of subacute glomerulonephritis in the nephrotic stage. He had marked papilledema and was practically blind. During the oral administration of renal extract his albuminuria decreased markedly, diuresis occurred, edema diminished and the blood pressure declined to a level only slightly above the normal. The vision improved rapidly so that he was able to read large print, whereas, previously he could not even see fingers, much less count them. However, since his illness was of only three months duration it is possible that the improvement in this patient may have been coincidental. Such an interpretation may be favored by the fact that the improvement in this patient was still manifest several months after treatment was discontinued. Since, in this case one might conclude either that the improvement was entirely spontaneous or that the extract was markedly beneficial, it is perhaps wisest to draw no conclusions.

We ourselves do not regard our results on patients as being convincing. The technical difficulties are great, many pounds of kidneys are required daily in order to treat one patient; and there is even doubt as to whether the active principle is absorbed at all in some subjects. Since, in rats, the preparations seemed to be several times as active when injected, as when administered orally, we are devoting our attention to the fractionation of the extract in an attempt to secure a potent nontoxic concentrate which can be injected without local or systemic reactions. Until this can be accomplished we prefer to draw no conclusions concerning the possible value of renal extract in patients.

The present status of the problem may perhaps be compared to that of the ovarian extract a dozen years ago. At that time the capacity of such extracts to produce physiological effects in small animals had been definitely demonstrated but the amount of the active principle present in the ovaries is so small that many years would have elapsed before the value of these preparations could have been demonstrated beyond question in patients, had not other sources been found from which the hormone was obtainable.

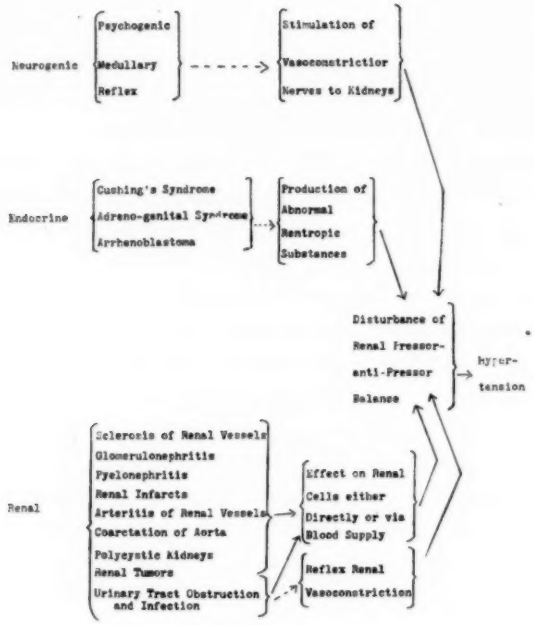

Figure 1

One would naturally wish to know whether these observations on the renal anti-pressor substance have any bearing on the general concepts of the genesis of hypertension. In this regard it may be emphasized that apparently favorable results have been obtained both in patients with "essential," and in subjects with renal hypertension. In view of this observation, as well as the others which have been mentioned, it may be justifiable to suggest that both the monogenetic theory and the polygenetic theories are partly true but that both are incomplete. Our present conception, which is still based largely on hypothesis, is illustrated in Figure 1.

There is some evidence, which can not be regarded as conclusive, that experimental neurogenic hypertension (e.g., that resulting from carotid sinus denervation or from intracisternal kaolin injection) is abolished by renal denervation and also that hypertension of this type may respond to the administration of the renal anti-pressor substance. It would therefore seem logical to infer that hypertension of neurogenic

origin, as observed in patients, may be mediated through a renal mechanism. (Obviously, this concept refers only to chronic hypertension and not to temporary elevation of blood pressure of nervous origin.)

The endocrine disorders associated with chronic hypertension are all characterized by the production of abnormal steroid compounds. Since it has been shown in experimental animals that many steroidal compounds exert a renotropic action and produce hypertension, it is not unreasonable to assume that the hypertension occurring in the endocrine disorders cited in the diagram is mediated through the kidneys.

Although the complete details of the mechanism of the chronic hypertension which results from primary affections of the kidney are still under discussion, few question its humoral basis and it is presumably brought about by a deficiency, either relatively or absolute, of the renal anti-pressor substance. Whether those disorders of the lower urinary tract which are sometimes associated with hypertension operate mechanically through effects on the renal blood vessels and parenchyma, or reflexly through a nervous mechanism analogous to that responsible for acute reflex anuria is still debatable.

If one accepts the validity of the concepts which have been outlined, it is possible to harmonize the monogenetic and the polygenetic theories of the pathogenesis of hypertension. It is quite possible that a number of separate primary disorders, whether of the nervous system, the endocrine glands, or of the kidneys, or of unknown origin, may all cause hypertension by acting on a fundamental renal mechanism.

Summary

The various theories which have been proposed to explain the pathogenesis of chronic hypertension in man are analyzed in the light of recent experimental findings in laboratory animals. The variety of clinical states which are associated with hypertension suggests a diversity in the mechanisms (polygenetic theory) responsible for hypertension. Recent experimental studies point strongly to the kidney as the site of the disorder (monogenetic theory). A schema is presented which attempts to harmonize these two divergent viewpoints and which, although hypothetical in many respects, appears to be in accord with available data.

Extracts of normal kidneys when administered to animals with experimental renal hypertension cause decline in blood pressure. The

administration of such extracts to a few patients with either renal, or so-called "essential" hypertension, has been followed in certain instances by decline in blood pressure and by clinical improvement. The possibility that the changes observed in patients may have been of spontaneous, rather than therapeutic, origin has not been completely excluded.

* * *

Although the results of the administration of renal extract to patients are perhaps of significance in regard to the mechanism of hypertension, they have no therapeutic importance at the present time. Until methods of obtaining a larger yield of the active principle and of producing purer extracts can be developed the results obtained with renal extract will be only of theoretical significance.

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THE USE OF INSULIN IN ITS VARIOUS FORMS IN THE TREATMENT OF DIABETES*

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THE use of insulin in its various forms in the treatment of diabetes is in its infancy. Insulin is not at all adequately appreciated and its application is not understood. The treatment of diabetes with insulin is still crude. To paraphrase Lukens' thought, we have constantly been trying to see how many diabetics we could treat without insulin rather than how many we could treat with it. What proportion of patients now secure its benefit, no one can say, but of the 14,153 diabetics registered in Berlin, according to Umber,[1] in 1940, the number using insulin was 37 per cent. In our own hospital practice 87 per cent received insulin and in the office practice 80 per cent. Moreover, few of us, who thank God and Banting and Best for the discovery of insulin and daily watch its miraculous action with our patients and are prescribing it more and more, would claim that we are using it to the greatest advantage or in the best way. And now, just before I shock you, as I myself was shocked, by recounting the dreadful examples of the disuse or improper use of insulin, I would call to your attention, in partial apology for the medical profession, that great discoveries in medicine percolate slowly. Opposite the hill on which I write these words is Charlton, in Worcester County, where was born one Thomas Morton who held his ether cone at the Massachusetts General Hospital for the first time in 1846. Yet two generations later in that same institution Harvey Cushing actually felt like giving up his medical career when the patient he was etherizing expired. The following recital is sombre, will be painful, but I believe should be said and I dare to do it because I report all my known diabetic deaths and strive to point out my own egregious mistakes. Do not be discouraged. We learn from our errors, and if we honestly describe them, one needlessly dead patient may lead to the saving of thousands of lives.

I repeat, insulin is not adequately used by the medical profession. A

* Read October 2, 1941 at the Stated Meeting of The New York Academy of Medicine.

physician of national reputation in the Middle West wrote me recently that within a period of four weeks this summer he had treated four doctors each with diabetic coma. This has happened in the face of the fact that a few years ago with the help of the Metropolitan Life Insurance Company it was possible to state that diabetic doctors from a study of their subsequent course lived longer than diabetics as a whole and that among all patients the mortality from diabetic coma has dropped from 63.8 to 3.6 per cent.

Upon one afternoon in September, 1941, three cases especially attracted my attention. The first concerned an interview with a friend of a diabetic child, living nearly two hundred miles away in a city of about 50,000 population, whose glycosuria was said to be of little account despite the child's hunger, loss of weight and strength. In the course of the consultation during my endeavor to see how I could coöperate with the doctor, the child's friend produced a bottle of a well-known quack medicine with which the child had been treated. A week subsequently I saw the frail, crying child arrived in acidosis with 9.0 per cent glycosuria, and this occurred nearly twenty years after the beginning of the use of insulin with human beings. That same afternoon another patient disturbed my equilibrium, because she was such a heavy weight for the modest elevator which brings patients to my office. Some months before, she was given insulin and told to protect the insulin with orange juice. During the period her weight rose from 225 pounds to 275 pounds. The third instance was a woman in middle life whose urine showed 4 plus diacetic acid and 6 per cent sugar. She had been given insulin about five weeks before, but the doctor, instead of instructing the patient, administered it himself twice a day, then died, leaving her without a knowledge of taking insulin.

During 1941 there have been at least eight deaths among our supposedly twelve hundred living patients with onset in childhood. Of these deaths at least two appear to me to have taken place because of hypoglycemia unrecognized and insufficiently treated.

Have I not told enough to demonstrate that the treatment of diabetes with insulin is in its infancy and that the use of insulin is inadequate and not understood? Let us now turn to a brighter picture.

The proof of the usefulness of insulin is best shown by the better maintenance of nutrition by diabetic children. It is so good, in fact, that their identity among their comrades is concealed. As a corollary to

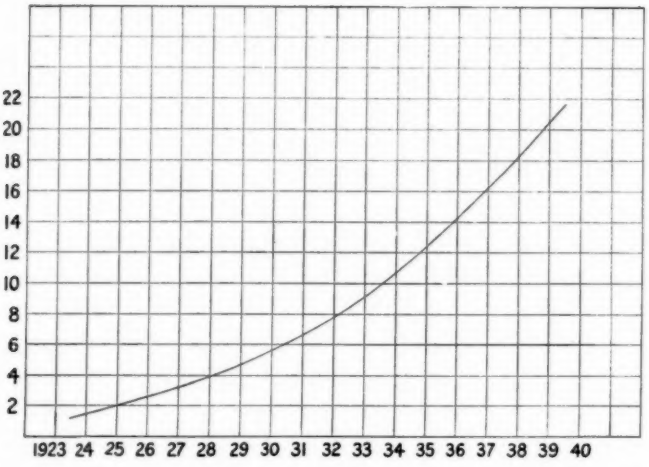

Chart 1—Nothing interferes with the increase in the distribution of insulin. (*Courtesy, C. H. Best.*)

this is their greater resistance to disease, not only to the chronic infections like tuberculosis, but to the acute infections and those requiring surgical intervention. By no means are these effects confined to children. The ability to bear the brunt of another disease running concurrently with diabetes is obvious to all. Whether neuritis and certain other complications are more frequent or less frequent is concealed by the longer duration of the disease and consequent longer exposure of the individual. Arteriosclerosis has ceased to appear as a rule at the end of five years, although it ranks first as the cause of death in diabetes.

Bodily efficiency and ability to work have increased so much since the use of insulin that the morale of the diabetic is completely changed.

The value of insulin is acclaimed by the uninterrupted increase in sales of the drug. So far, nothing has interfered with this upward tendency. Despite the subcutaneous method of administration which makes so many apprehensive and delays its employment, there is an increasing readiness to use and inject it.

The efficiency of treatment and the standardization of the disease are more readily accomplished with the aid of insulin than in any other manner. It is far simpler today to compare results of different methods of treatment, thanks to insulin.

The diffusion of knowledge of the physiology and the pathology of diabetes has greatly expanded since the introduction of insulin and constitutes one of the long range benefits from its discovery. It has raised the platform of knowledge of diabetes and metabolic processes in the body in the minds of millions of people. It has created respect for scientific work in laboratories such as perhaps no other achievement.

I will not burden you with statistical evidence showing the improvement of treatment of the disease save for a few examples. The first group of these is made up of the 83 cases who were the first to receive insulin at our hands. Of them 50 have died, and the average duration of life of these fatal cases was 10.3 years. Thirty-three still remain alive and the average duration that they have attained is 20.7 years. Since the previous computation one year ago there have been no deaths.

The second group. Fifty of our diabetics under the age of 40 years with a duration of the disease of at least five years were studied in 1930 intensively by H. C. Shepardson of San Francisco. Of this group, 12 have died and their duration of life has been 13.3 years. The duration of life of the surviving 38 on the average is 19.8 years. During this last year there have been no deaths.

The third group. Diabetes with onset in childhood of twenty or more years' duration. At present there are sixty-two children eligible for this classification. Of this number two have died after a duration of the disease of twenty years and the causes of death have been coma and streptococcus sepsis. Of the remainder, we have thus far definite information that 59 are living in 1941 and have reason to suspect that the one untraced also is alive, because they were all traced in 1940. It is very much more difficult to trace a diabetic child now than formerly, particularly those with such long duration, and obviously the girls because so often names are changed.

The fourth group. The total number of fatal cases between January 1, 1937 and March 29, 1940 which we chance to know was 927. For these the average duration of life was 12.5 years. Prior to the discovery of insulin my patients lived 6 years and their age at death was 46.7 years instead of 64.8 ending in 1940. The life expectancy for a ten-year-old diabetic child as calculated for me by the Metropolitan Life Insurance Company was such that he would reach his fiftieth birthday and, in fact, for all ages was approximately two-thirds that of the population as a whole. The number of patients now living for 12 or more years is so

large that it obviously makes the computation of statistics unusually difficult, because of change of residence or name.

Statistics relating to pregnancy are striking. To the mother pregnancy carries very little greater mortality than for non-diabetics. For the offspring, under most modern conditions of treatment, the viability is about 90 per cent for those whose mothers have had prolan determinations which were normal or if abnormal were corrected by hormones.

Diabetic mortality statistics I fear may grow less accurate as years advance. This is readily explainable because so many of the patients succumb to diseases which are not definitely related to diabetes and thus the diabetes fails to appear on the death certificate and also because the disease diabetes is so mild at death that it may not claim recognition at all, even by the family physician. Thus far, the incidence of diabetes has been almost steadily rising, and from twenty-seventh as the cause of death in 1900 for the United States it was ninth in 1938, but in 1939 became eighth with the prospect of displacing both pneumonia and tuberculosis in the near future. It would then become sixth as the cause of death and only exceeded by cancer, arteriosclerosis in its various sites, and deaths by violence. Plainly, diabetic statistics in the future must depend upon those of private clinics, and those especially sought by detailed investigation. Insurance companies could help to disclose the knowledge of the causes of death of diabetics perhaps more readily than is possible in any other way than those just cited. I fear that we may become blinded to the growing importance of the disease by a halt in its mortality incidence. Thus, in the seventh month of 1940 the death rate from diabetes among the Metropolitan Life Insurance Company policy holders in their industrial departments was 30.2 per 100,000, but in 1941, 29.3 per 100,000. I confess I shall become skeptical about the accuracy of diabetic statistics if the incidence does not go up. My experience in comparing the reputed incidence of diabetes in Arizona with that in Rhode Island[2] taught me that although in one state the reported incidence is 10 compared with 42 per 100,000 in the other, I was able to satisfy myself by detailed investigation that the actual mortality rate in the two states was approximately the same, if one made allowances for age and sex of the inhabitants on the one hand and the ability to secure data from them on the other.

And right here may I put in a plea for more autopsies, or rather published records and analyses of autopsies of diabetics. Shields War-

ren[3] in the second edition of his book bases his studies upon 486 autopsies. Weichselbaum[4] in 1901 reported 18 cases. Gibb and Logan[5] in 1929 reported 147 autopsies. When we recollect that in 1938, 31,037 people died with diabetes in the United States and in 1939, 33,395, the paucity of data upon which to base conclusions upon the pathology of the disease is evident. How many autopsies were reported, and analyzed, upon diabetics in New York City in 1940? The new American Diabetes Association and its subsidiaries can be of great service in collecting data of this type.

Regular Insulin. Until the present, most of the advantages of the treatment of diabetes with insulin can be ascribed to regular insulin. Protamine insulin came into use during 1936, but since that date the average age at death of my patients has advanced only from 63.6 to 64.8 years, and the duration of the disease from 12.1 to 12.5 years ending March, 1940. There are certain exceptions to the above statements. It is true coma has dropped still further, but it was already low.

Regular insulin exerts an action for six hours, and save with those patients whose disease is so mild that the blood sugar falls to normal during the night it is necessary to give four doses in twenty-four hours to control it. Boyd[6] has shown that even hepatomegaly could be obviated if such a general rule was followed. If only one type of insulin was available one would choose regular insulin, or rather its counterpart, crystalline insulin, which apparently acts just the same only for about an hour longer. If one wished adequate control of the disease, save in those mild cases becoming sugar-free during the night, the largest dose would be given before breakfast and attempts made by rearrangement of the diet to avoid a dose at noon, the second injection before the evening meal, and the third toward midnight, consisting of a few units varying with the urinary tests. Each dose omitted, even that at noon would mean that doctor and patient were contented with a passing mark and were not striving for a Phi Beta Kappa key or, better, perfection. Perhaps 24-0-18-2 would represent the dosage which has generally been used by those physicians almost meticulous in the care of their patients, but for complete protection a slight amount at noon would be generally needed.

In diabetic coma the need is for insulin, and the dosage rises the longer the duration of the coma before treatment begins and the greater the severity of the acidosis. The sky is literally the limit, and just because one does not recover with 500 or 1000 units is no excuse for not admin-

istering 1500 or 2000 units if the case warrants. The need in coma for liquids to combat dehydration stands next to the need for insulin, and this, too, varies widely from an average of 2000 cubic centimeters to the exceptional patient who recovered with 11,000. We never have had reason to fear circulatory collapse following the parenteral administration of insulin.

By no means is the short duration of the action of regular or crystalline insulin its only drawback. As a matter of fact, at least for approximately half of its effective period, it is over- or underactive, because a preliminary time is required for it to exert an adequate effect and later despite careful adjustment of food with the insulin, hypoglycemia can easily result.

The disagreeable qualities of any insulin are included in the action of regular insulin. First and foremost come insulin reactions. In not a single instance since the introduction of insulin on August 7, 1922 have we known of a death clearly due to hypoglycemia in a patient treated with insulin who was already in, or brought into the New England Deaconess Hospital. One unconscious patient was admitted. He remained unconscious for days and finally died, but we are still in doubt after the autopsy as to whether that patient died from hypoglycemia. On the other hand, insulin reactions certainly are responsible for more deaths from diabetes than are recorded on death certificates. This is not because there is falsification of the death certificate, but rather due to an error on the part of a physician. In a recent article in the *Medical Clinics of North America*, I have discussed this in detail. My experience has led me to conclude that if recovery during a possible insulin reaction does not occur within 15 minutes the patient should be taken to a hospital unless facilities for tests of the blood are available in the immediate vicinity.

The difficulty in distinguishing between an insulin reaction which has gone on for an indefinite time and late diabetic coma is very great. In that same article four or five needless deaths from hypoglycemia are described. It is a safe assumption that no insulin can be invented which will not lead to an insulin reaction provided exercise is unusual and diet omitted. Insulin atrophies occur with regular insulin and with protamine zinc insulin with uncertain frequency. Whether they will develop with the other types of insulin, one can tell only when a large number of cases have been treated with these. Notable insulin atrophies occur per-

haps in one in a hundred or even one in fifty cases and still more frequently in children. Consequently, one must have experience with several hundred, indeed several thousand cases with the newer types of insulin before a conclusion can be drawn regarding the same. Insulin indurations or lumps depend almost entirely upon neglect to follow the standard rules for treatment, namely, to distribute the dose of insulin over various sections of the body and never to administer two injections within an inch of each other in the course of a month.

Insulin Sensitivity. Unquestionably I think it can be said that insulin sensitivity is somewhat less with crystalline insulin than with regular insulin. Whether it will be entirely absent with the other types of insulin to be discussed later will depend upon the accumulation of hundreds or thousands of cases. At any rate, in the last few months we have been less concerned about insulin sensitivity, because apparently one can relieve the severe forms of it very simply by beginning with injections of 1/1000 part of a unit and increasing by 1/1000 of a unit at each injection, four times a day. As a rule, after 24 hours it will be found that the rate of increase can be accelerated so that within two or three days it is possible to give several units. During this interval of waiting, one treats the patient as in the days before insulin was discovered by lessening the need for calories by rest, by curtailing nutrition through decrease of fat, reduction of protein to a gram or ⅔ of a gram per kilogram body weight and lowering carbohydrate, at least to 100 grams in 24 hours.

The outstanding effects of regular insulin are shown best of all in the decrease of deaths from coma by prevention or actual cure and, second, by the lengthening lives of diabetics with onset in childhood.

Crystalline insulin is a solution of zinc insulin crystals. Its action is essentially the same as that of regular insulin with one exception, namely, the duration of the effect is about one hour longer. The type of reaction is essentially the same as that caused by regular insulin. Insulin atrophies can occur. Insulin induration will develop in the careless patient. Insulin sensitivity likewise appears although possibly a trifle less than with regular insulin. It can be overcome by the same measures as recommended above. To me, the effects of crystalline can be summed up in the words that it is a purer drug than regular insulin, has all the advantages of the former with somewhat less of its disadvantages, costs no more and with the same frequency of doses a patient can be controlled for an additional three hours in the 24 hours.

Protamine Insulin and Protamine Zinc Insulin. Hagedorn revolutionized the treatment of diabetes when he added protamine to insulin and thereby doubled the duration of its action. This was quickly changed by Scott, who, by the addition of zinc doubled again the action of protamine insulin, prolonging its effect for fully 24 and possibly even to 48 hours. At any rate, Marble and Bailey found that satisfactory tests could not be undertaken with a new type of insulin until protamine zinc insulin had been omitted for that period. Protamine zinc insulin reduced the number of injections for the patient, made treatment safer, simpler and more agreeable, encouraged more doctors to give it and patients to begin it, kept the disease under control for a longer period, and in cases of moderate severity one dose a day has been sufficient. The overlapping effect from day to day of protamine zinc insulin and the necessity of taking a few days' time to transfer a patient from crystalline insulin to it I consider of no importance. Two or three days will not count in the length of a diabetic patient's life today. Furthermore, most of us today begin treatment with protamine zinc insulin and therefore there is no time lost in the transfer.

Protamine zinc insulin acts while you sleep and that is not a disadvantage if a patient understands it and guards against it by a supplementary meal on retiring. Certain patients do not need this. It is particularly adaptable to severe diabetics who day and night show glycosuria from endogenous metabolism. Protamine zinc insulin, therefore, with quick-acting crystalline insulin administered before breakfast to help utilize the food consumed, gives us a method for treating the severest diabetics and I do not worry about its application to the milder. As a matter of fact, among three hundred hospital diabetics, treated in succession in 1938, for whom McDaniel of our clinic compiled for me the intake of insulin, it was found that 10 per cent required no insulin whatever, 39 per cent were regulated with an average dose of 22 units of protamine zinc insulin, whereas 50 per cent required both crystalline and protamine zinc insulin before breakfast, 13 units of crystalline and 39 units of protamine.[7] Reading the very excellent article by Marks[8] which appeared in the *Medical Clinics of North America* of May, 1940, one can learn how in perhaps considerably more than our 39 per cent, it is possible by adjustment of diet to regulate the patient with a single dose of protamine zinc insulin. I commend this article to your attention. On the other hand, I must say that of the cases cited with

successful treatment with a single dose, not one was a child, and we have found that with our children it was practically always necessary to give a quick-acting insulin along with the protamine zinc insulin.

Adjustment of the diet of the insulin-using patient is desirable. Practically all our patients for years have had approximately carbohydrate one-fifth for breakfast, two-fifths at noon and two-fifths at night, taking away 5 or 10 grams of carbohydrate from their noon or night meal to use between meals or upon retiring. This was for those cases in which it seemed likely that a low blood sugar would arise during the night. We have taken advantage of Pollack's advice and given more protein with that retiring meal.

Protamine zinc insulin is well adapted for use during infections, and at the time of surgical operations. One does not attempt to control the entire disease with protamine zinc insulin on such occasions, but in protamine zinc insulin one exerts a steady, partial control of it and can supplement it with quick-acting insulin every four or six hours according to tests of the urine.

Since the introduction of protamine zinc insulin it is a fact that we have given up our wandering diabetic nurse, going from home to home, because we no longer needed her. Already I have called attention to the lessening number of patients with diabetic coma. Furthermore, those patients who do develop coma develop it because of gross irregularity for which protamine zinc insulin could in no way be held responsible. The disappearance of hepatomegaly was striking. Marble, White and all our group felt almost sorry that we did not have a chance to try lipocaic, because when protamine zinc insulin was introduced, the large livers of our children right under our fingers and eyes by x-ray went back to normal. Dwarfism in diabetes is now a very, very rare occurrence. Of course this may be due in part to the more liberal diets which we give, stimulated in their use by reports from clinics in Vienna, California and your own Geyelin.

A word more about office treatment. Today it is extremely difficult to secure an adequate number of beds at the hospital for our diabetic patients. The number, therefore, treated in the office of necessity has definitely increased. Willingness to do this is largely due to a feeling of greater safety, as well as ease of administration, of protamine zinc insulin.

From all these favorable remarks about protamine zinc insulin, you might infer that I do not realize its disadvantages. It is unfortunate that

protamine zinc insulin is a cloudy mixture. To me it is extraordinary that protamine zinc insulin works as well as it does when one considers that unless the bottle is manipulated in exactly the same way for exactly the same number of seconds and the insulin withdrawn in the same period of time, one must have variation in the actual content of the mixture injected. Any type of insulin which depends upon the injection of solid particles in suspension in a liquid admits of improvement. The second objection is the considerable number of patients who show localized reactions lasting from a few days to a few weeks following its use. Almost invariably these will disappear if one persists in treatment, but I have seen cases in which we have changed from one type of protamine zinc insulin to another and, I think, in one instance have given it up and returned to a quick-acting insulin. A third disadvantage of protamine zinc insulin is its slow action which does not allow it to utilize the carbohydrate at breakfast even if that contains but one-fifth of the carbohydrate for the day. As mentioned, it was efficacious for 39 per cent of our patients, but in approximately one-half it was not. It is because of these three disadvantages of protamine zinc insulin that we welcomed the opportunity and felt deeply honored that the Eli Lilly Company and Burroughs Wellcome and Company invited us at the George F. Baker Clinic to test simultaneously, using the same standardized patients for a background, clear protamine zinc insulin, histone insulin and globin insulin. You will at once recognize, as did we, the high motives which actuated the action of these two manufacturing concerns and the standard thus set for other therapeutic investigations, and I trust the authorities in Washington will take cognizance of it.

This work has been carried out during the last nine months under the supervision of Alexander Marble and C. Cabell Bailey at the George F. Baker Clinic at the New England Deaconess Hospital. It would be wrong, even if there was the time, for me to give the details of their work, because it is their work and not mine, and although completed, not yet published. Naturally I have been conversant with it because it has gone on under my eyes, but it is to them and them alone that I am indebted for the privilege of calling your attention to certain conclusions which they reached and how they reached them. I hope you realize my obligation to the manufacturers of these new insulins, as well as to other recent investigators.

Experience gained by Marble in his study with Vartiainen of the

relative merits of regular and crystalline insulin in 1939[9] was most helpful, and many of the methods then followed were employed. In general the conclusions of Marble and Bailey have been confirmatory of the reports hitherto published.

Three methods of procedure were adopted, first an intensive study of five volunteer patients, four males ages 19 to 32 years and one female age 47, to whom we all are greatly indebted. They remained in the hospital solely for the investigation for consecutive periods of 74 to 132 days. All had had diabetes for ten or more years, save one for 9.3 years. The diet for each patient was constant throughout, the carbohydrate ranging from 152 to 211 grams. The urine was tested qualitatively seven times daily and the sugar and nitrogen quantitated in the 24-hour quantity. Five blood sugar tests were made each day. Each type of insulin was employed from 7 to 32 days with each patient.

Two types of experiments were made with each of these five patients. Of these, the first was an estimation of the action of the special insulin under study during a day of fasting, begun with a subcutaneous injection of 0.15 to 0.2 unit per kilogram body weight, or 7 to 11 units. Upon these days blood sugar tests were made at 8 A.M. and half an hour later, and thereafter from 9 A.M. onwards hourly until midnight and again at 8 A.M. the following morning. In all, ten such fast days were made with histone zinc insulin, ten with globin zinc insulin, nine with clear protamine zinc insulin, six with crystalline insulin and four with turbid protamine zinc insulin, invariably using insulins of U-80 strength.

The other type of experiment with these five hospital patients was the observation of the effect of the various insulins over a period of days.

The second major plan of investigation was with twenty-one hospital patients upon whom the effect of the various insulins was watched over considerable periods.

The third group consisted of patients who continued, in their homes, the use of the various insulins which they had begun in hospital.

Histone insulin is insulin to which histone, a simple protein obtained from the thymus, is added. It was first described by Biasotti and coworkers,[10] and later by Gray, Bischoff and Sansum,[11] and most recently by Barnes, Cuttle and Duncan,[12] who used a preparation made by the Eli Lilly Company to which zinc had been added. The last group obtained better results with it than with regular insulin or protamine zinc insulin. It was furnished us by the Eli Lilly Company. It is a turbid insulin

pH 7±, the added protein is 3.2 mg. and the zinc content is 0.2 mg. per 100 units.

Globin insulin, first prepared by Reiner, Searle and Lang,[13] consists of insulin to which a simple protein globin, made from red blood corpuscles of beef blood from which the iron containing fraction has been removed, is added. Its action was described to be more than twice that of regular insulin, giving results approximating or even better than protamine zinc insulin. It has been extensively studied and reported upon in publications by Bauman,[14] and also by Andrews and Groat.[15] It is a clear insulin, pH 3.7, the added protein is 3.75 mg. and the zinc 0.31 mg. per 100 units. This was furnished us through the kindness of Burroughs Wellcome and Company.

Clear protamine zinc insulin was also furnished us by the Eli Lilly Company, first, in fact, some four years ago. It has salmon sperm as the source of the protein, a pH of 3.3 – 3.5 and the added protein is 3.8 and the zinc 0.31 mg. per 100 units, and more glycerin than in turbid protamine zinc insulin.

A. Fasting Tests. Histone zinc insulin was given on two occasions each to five patients at 9 A.M. who had gone without food since the previous evening and who continued to fast for the following 23 hours. From the composite curve of the ten experiments it is evident that the effect began in half an hour, produced within two hours an initial fall of the blood sugar of 45 mg., possibly due to soluble insulin in the mixture, which continued with lessening force up to, at least, 15 hours, but with some effect still persisting at 24 hours.

Globin zinc insulin. The composite also of ten fasting day experiments showed that the effect began in one hour, the fall in blood sugar being rapid until the eighth to tenth hours and then more gradual until, at least, the fifteenth hour, followed by a slight but definite rise at 23 hours.

Clear protamine zinc insulin, like globin insulin, began to act in an hour, reaching the lowest blood sugar level in ten to eleven hours and then remained constant until the thirteenth hour and thereafter showed a definite rise up to the twenty-third hour.

For comparison I insert the curves for crystalline, turbid protamine zinc insulin and histone zinc insulin published by Barnes, Cuttle and Duncan.[12]

B. Maintenance Tests. A single dose of the respective insulin to be

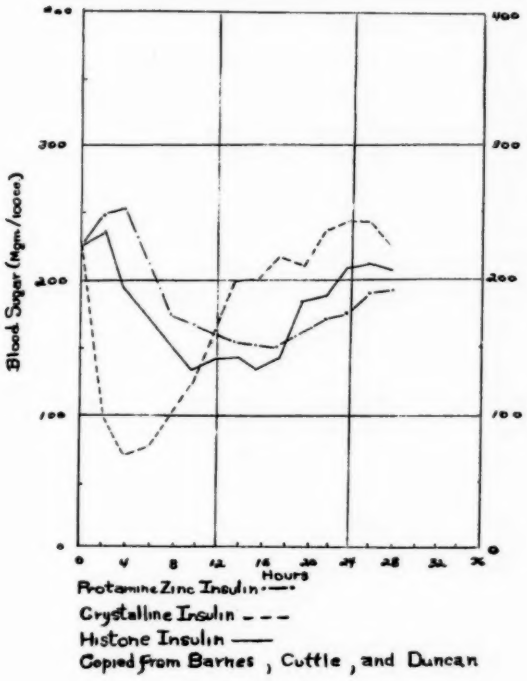

Chart 2

studied, often replacing two injections of crystalline and protamine zinc insulins, was given four of the five volunteer patients daily for 7 days and the customary 7 specimens of urine and 5 samples for blood sugar analyzed daily. Under less carefully controlled conditions other hospital patients were studied: nine with histone, seven with globin and a similar number with clear protamine zinc insulin.

Histone Zinc Insulin—Maintenance Tests. With this insulin the diabetes was well controlled. The fasting blood sugars were normal. There was a slight rise in blood sugar between 7 and 11 A.M., followed by a further rise between 11 A.M. and 2 P.M.; thereupon it fell until 5 P.M., rising again until 10 P.M. and then falling during the night. A bedtime lunch was given in all cases.

The maintenance tests with globin insulin indicated the need for three meals and an afternoon instead of a bedtime lunch. The fasting blood sugar values were usually normal. Between 7 and 11 A.M., the

blood sugar rose on the average 90 mg., between 11 and 2 it rose or fell slightly and between 2 and 5 it fell moderately (av. 27 mg.) or greatly (av. 140 mg.), depending upon whether a mid-afternoon lunch was given the patient, followed by a slight fall until 10 P.M. and the next morning usually a normal blood sugar.

In the maintenance tests with clear protamine zinc insulin, the fasting blood sugar was usually high, indicating a lack of sufficient action for 24 hours. The blood sugar rose between 7 and 11, which possibly might have been partly avoided if the insulin had been given at a longer interval before breakfast. It fell between 11 A.M. and 2 P.M. with an average fall of 38 mg. The fall between 2 and 5 P.M. depended upon whether a mid-afternoon lunch was given and was comparable to that of globin. The blood sugar remained constant between 5 and 10 P.M., tending to rise during the night. For good results an afternoon lunch was required, but a night lunch was not needed, and, indeed, was prejudicial to good effect. In general, regulation was difficult.

In maintenance tests with turbid protamine zinc insulin, the fasting blood sugars were always normal, an evening lunch usually being required. From 7 A.M. to 11 A.M. and 11 A.M. to 2 P.M., there was a continued rise of the blood sugar; thereupon a fall of an average of 67 mg. until 5 P.M. and a lesser fall in blood sugar up to 10 P.M.

C. Clinical Trials. With histone zinc insulin these resulted favorably with the seven cases tested, especially with the two children, 11 months and 2 years old respectively. The other five cases averaged 22 years of age. This favorable action is especially noteworthy, because the histone cases (barring the two infants) averaged 22 years of age as compared with the globin cases who averaged 41 years and the clear protamine zinc insulin cases who averaged 37 years. However, as much as I would like to do so, I must caution against drawing too favorable a conclusion from the excellent action of histone zinc insulin in replacing injections of both crystalline and protamine zinc insulin with the very young children 11 months and 2 years old respectively. Young children with diabetes of short duration often have low blood sugar values early in the day.

Globin zinc insulin worked still better in the clinical trials in the 21 hospital cases and in the patients' homes than with the five special study cases in the hospital. Provided an afternoon lunch was given, afternoon reactions were eliminated. One patient alone had a night re-

action, avoided later by a bedtime lunch. Globin insulin did not act favorably with one child of 21 months. Attention has been called to the average age of the globin patients being 41 years, thus conforming to the ideas of others who have worked with it, that it is especially of value with patients of middle age or older, i.e., with diabetes of moderate rather than extreme severity.

Clear protamine zinc insulin did not act as favorably in clinical trials as histone or globin insulin. The average age of the patients tested was 37 years. However, it should be said that four patients have been maintained upon it successfully since 1937.

Conclusions

For these I alone am responsible. If restricted to the use of a single insulin I would choose crystalline insulin, because it is the purest of all the types, is a clear insulin, acts promptly and therefore is indispensable in diabetic coma and can be given frequently enough and in sufficiently variable doses to control any type of diabetes throughout the twenty-four hours.

Next to it I would place protamine zinc insulin, because it acts so long that it is a constant protection for the patient against the vicissitudes of life. That one day's dose overlaps another for one or possibly two days is advantageous. Moreover, in about 40 per cent of the patients one daily dose before breakfast controls the disease and this percentage could probably be raised with careful adjustment of diet. Histone, globin and clear protamine zinc insulins have certain advantages over protamine zinc insulin, but not as yet sufficient to displace it.

Histone insulin combines to some extent the prompt action of crystalline with the prolonged action of protamine zinc insulin so that in an increasing number of cases one dose of it will replace the injection of crystalline insulin so often necessary to supplement protamine zinc insulin. It is possible it will serve in this way in very young children. Histone insulin causes few reactions and so far no allergic local phenomena have been reported. It has the fault of being a turbid insulin with the possibility of uneven distribution of the insulin precipitate, particularly in higher concentrations.

Globin zinc insulin is a clear insulin, produces so far as reported no allergic reactions, acts less promptly than crystalline and a little less promptly than histone insulin, but much more promptly than protamine

zinc insulin, and if an afternoon lunch is given, causes few reactions. Its effect lasts for about twenty-four hours.

Clear protamine zinc insulin is similar in action to globin insulin, but so far in our hands is not so uniform in action as globin insulin or as the other insulins.

In my opinion, a single dose of histone or globin insulin will control rather more diabetics than a single dose of protamine zinc insulin, but the difference is as yet so slight and the possibilities so good for overcoming the turbidity of histone insulin and the delayed action of both histone and globin, particularly globin, that it would seem definitely inadvisable to complicate the treatment of diabetes by introducing either upon the market in their present state. I think we have the right to expect that an insulin superior to protamine zinc insulin will be available to diabetics at some time in the future. In the meantime, both doctors and patients should more assiduously strive to control diabetes by better adjustments between exercise, diet and the excellent insulins now available.

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DIABETES IN PREGNANCY*

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BEFORE insulin was available conception was rare and when it did occur, there was a marked fatality in both mother and child.[1] Since the introduction of insulin the maternal hazards have diminished a great deal but the fetal mortality continues high. Measures are not exhausted that may lead to the solution of the present problem without recourse to risky or complicated procedures, that are much in vogue at the present time, such as cesarean section or endocrine therapy. Two possibilities that promise much have not received full consideration thus far in the management of pregnancy in diabetic women. These are: careful control of diabetes from the beginning of pregnancy and during its entire course, and, the effect of protamine zinc insulin in contrast to that of the unmodified, or regular insulin. When these two means of treatment will be completely worked up and applied, it may be that most, if not all, of the complications occurring in diabetes pregnancies will be set aside.

The relation of diabetes mellitus to pregnancy will be discussed under three headings:

1. Effect of pregnancy on carbohydrate metabolism.
2. Effect of diabetes upon the pregnant woman.
3. Effect of diabetes upon the fetus and the newborn infant.

EFFECT OF PREGNANCY ON CARBOHYDRATE METABOLISM

Renal glycosuria

A lowered renal threshold to the blood sugar commonly occurs during pregnancy. This consists of a leakage of sugar in the urine while the utilization of glucose within the body takes place in normal fashion. In itself, it is a harmless anomaly unless the glycosuria becomes intense, when through loss of large quantities of sugar it may induce acidosis

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and, consequently, give trouble. However, this is a very rare event and is one of the curiosities in medical or obstetrical practice. When renal glycosuria complicates a true diabetes, it may add serious difficulties in the control of the diabetes because of the loss of an exceedingly large amount of sugar in the urine. Under such circumstances the best has to be made of the situation and the blood sugar kept at as low a level as possible without causing hypoglycemic reactions. The aim in managing such a dilemma is that enough glucose will be metabolized to maintain normal nutrition regardless of the amount of sugar lost in the urine. This can usually be accomplished with careful supervision and regulation.

The differential diagnosis between renal glycosuria and diabetes may be somewhat difficult, but usually the existence of glycosuria while the blood sugar is at a level of 170 mg. per 100 cc. or less, justifies the diagnosis of renal glycosuria. Glucose tolerance tests may be misleading since in many cases diabetes and renal glycosuria co-exist. However, if the glucose tolerance is normal then the glycosuria may be taken to indicate that renal glycosuria alone is at fault and that diabetes is not present.

Onset of diabetes during pregnancy

This has been reported frequently. Williams[2] reports 9 women in whom the first symptoms of diabetes developed after conception; Herrick and Tillman[3] found that in their 67 cases of diabetes complicating pregnancy, 15 began during pregnancy. Wilder[4] notes that cases of true, severe diabetes arise in pregnancy. These and similar findings mean that the strain of pregnancy may change a latent diabetes into an active one.

Clinical course of diabetes in pregnancy

As a rule, there is an exacerbation of diabetes throughout pregnancy, that is, carbohydrate tolerance diminishes and insulin requirement increases. During labor the carbohydrate tolerance usually improves and the need for insulin is decidedly less. After delivery the diabetes generally ameliorates and returns to the state it was in before pregnancy began. These are the accepted generalities regarding the effects of pregnancy upon diabetes, but it is not safe to rely upon them for absolute guidance in the management of the individual case. Unpredictable variations in the severity of the diabetes do occur and may be of vital con-

sequence not only to the expectant mother but especially to the fetus. Therefore, it is worth making an analysis of reports on the clinical course of diabetes in the first, second and third trimesters, during labor, and after delivery.

First trimester. During this period carbohydrate tolerance is likely to be decreased according to Herrick and Tillman.[3] A progressive decrease in carbohydrate tolerance during the entire pregnancy has been noted by Allen[5] and by Hurwitz and Irving.[6]

Second trimester. During this period there is, as a rule, little change. In some cases there is an abrupt decrease in carbohydrate tolerance and a corresponding sudden increase in insulin requirement. This was noted in 3 cases by Herrick and Tillman[3] and was found by Hurwitz and Irving[6] at about the fifth month. These sudden shifts in the severity of the diabetes must be met promptly if harm shall not come to both mother and fetus. Consequently, Herrick and Tillman[3] give the sound advice that during the second trimester the cases should be checked every 7 to 10 days.

Third trimester. Insulin requirements may diminish during the last trimester. The supposition is that the pancreas of the fetus supplies some insulin at this time, supplanting to a certain extent that furnished by the mother. On the other hand, Allen[5] finds that carbohydrate tolerance diminishes during the third trimester. Herrick and Tillman[3] state that marked changes in tolerance may be expected. Out of 20 patients, 9 gave evidence of very definite improvement in the diabetes status, 7 showed a decrease in carbohydrate tolerance, while 4 remained unchanged. A decline in tolerance over even a short period of time may result in the destruction of the fetus. Hurwitz and Irving[6] observed one case which became sugar-free 10 days before term without insulin, after a previous requirement of 60 units per day. Consequently, the frequent checking of the diabetic pregnant woman and making suitable insulin and dietetic adjustments during the third trimester as well as during the second, is imperative.

Just before delivery. During labor an increased glucose tolerance is often noted. This may be due to increased activity of the voluntary muscles and to uterine contractions. On the other hand, an exacerbation of the diabetes and acidosis may develop and prove to be of serious significance to both mother and child.

Postpartum. The insulin requirement usually diminishes. According to

TABLE I

	Single		*Married and Widowed*	
	Male	*Female*	*Male*	*Female*
Diabetes deaths, persons 45 years and over	63	53	547	1,196
Population, persons 45 years and over	82,494	82,450	644,285	643,827
Death rate per 100,000	76.3	64.3	84.9	185.7

New York City. Diabetes—Death and Death Rates—Older Adults, by Civil Condition. Average 1931 and 1932. (Courtesy of Dr. C. B. Bolduan)
Diabetes deaths in persons 45 years and over are most frequent in married and widowed females, indicating that: *Pregnancy increases the liability to Diabetes.*

Allen[5] this is the first time this occurs since the beginning of pregnancy.

The marked variations in carbohydrate tolerance, in the severity of the diabetes and in the insulin requirement, make it evident that careful control of the diabetes from the very beginning of pregnancy to its termination is necessary to prevent the disastrous effect such sudden changes in the carbohydrate metabolism may have upon both mother and fetus. Very few authors stress this fact. Herrick and Tillman[3] insist on it and it may be that the good results they obtain in cases of diabetes in pregnancy, may be attributed largely to this method of controlling the diabetes.

The role of pregnancy in the production of diabetes in later life

The diabetes death rate, which really indicates the incidence of diabetes, is increasing more in females than in males. The increase is almost entirely in females over 45 years of age. It is interesting to note that diabetes deaths in persons over 45 years of age, occur at about the same rate in single males and females, whereas in the married and widowed, the death rate of females is far greater than that of males (Table 1). (The above data compiled by Dr. Charles F. Bolduan of the New York Department of Health have not been carried beyond the year 1932 because until the 1940 census figures are available, accurate rates can not be calculated.) From these facts it would appear that pregnancy increases the liability to diabetes. Joslin,[7] in discussing these findings, stated that he observed that the average weight of his married

female patients above 45 years of age, was 181 lbs. as compared with a weight of 161 lbs. in single women. Consequently, he believes that the greater tendency to obesity of married females is responsible for the more frequent occurrence of diabetes in this group. Bolduan and I are still of the opinion that pregnancy is a predisposing factor in the development of diabetes after 45.

Acidosis

Acidosis is acknowledged as a common cause of fetal death in diabetes pregnancies (Herrick and Tillman;[3] Wilder;[4] Hurwitz and Irving[6]). Acidosis develops when the diabetes is neglected and is poorly controlled. The advisability of frequent checkups previously mentioned, becomes evident. It was also noted that the shift in carbohydrate tolerance may be sudden and that it has to be compensated for almost immediately if serious complications are to be prevented.

The case report of a 19 year-old diabetic primipara (Massachusetts Medical Society, Section of Obstetrics and Gynecology[8]) is worthy of note in this connection. This patient became unconscious because of acidosis after she went into labor, stillbirth followed, the mother survived. The report concludes: "Until diabetes in pregnancy can be controlled better than it is at present, any patient with severe diabetes who goes beyond 37 weeks with a viable child, stands a definite chance of losing the fetus by intrauterine death unless labor is induced or a cesarean section performed."

This drastic recommendation for induction of labor or cesarean section is based on insufficient grounds. If this patient had had adequate supervision by a doctor who understood the treatment of diabetes, coma should not have occurred and acidosis should have been remedied when it began, a number of hours at least, before "impending coma," let alone unconsciousness, developed. The institution of intensive treatment for diabetic acidosis, only when the patient became unconscious, is an admission that the diabetes was poorly supervised and the recommendation of routine cesarean section would seem a very radical remedy to forestall such a mishap. The mode of action suggested, i.e., that the diabetes specialist carry out frequent blood sugar estimations and prevent actual unconsciousness during labor, does not meet the aims of treatment in diabetes, nor does it fulfill the needs of the patient. Much more is required and it becomes evident that the attendance of a physician well

versed in handling diabetes, is necessary not only during labor, but throughout pregnancy.

Hyperglycemia

A high blood sugar in itself, without concurrent glycosuria, is, in all probability, of no significance,[9] since under these circumstances, all the ingested sugar is metabolized and there is no loss in the urine and, as might be expected, there is no increased tendency to infection or other complication. On the other hand, if the glycosuria is marked, signifying the loss of a large amount of sugar to the body, then the results may well be disastrous. Under these circumstances, acidosis, protein destruction, loss of sodium and dehydration make themselves felt and, doubtlessly, have a serious effect upon the mother and often result in fetal death.

The use of protamine zinc insulin may modify the views we have held concerning the significance of glycosuria. This form of insulin results in adequate assimilation of sugar throughout the 24 hours in spite of the occurrence of glycosuria. In the treatment of non-pregnant diabetics, it is freely acknowledged that small amounts of sugar—10 to 20 grams per day—in the urine of diabetics are not harmful. Tolstoi and Weber[10] have gone a good deal further than this and have claimed that the occurrence of large quantities of sugar in protamine zinc treated diabetics are of no consequence provided there is a liberal carbohydrate intake. Their case reports ring true but are so far removed from our previous conception of what adequate diabetes treatment consists of, that they have been accepted with some hesitancy until further proof is forthcoming. However, it must be remembered that for the first time a form of insulin is available that will regulate the carbohydrate metabolism throughout the entire 24 hours, resulting in both assimilation of glucose as glycogen, and the oxidation of glucose in spite of the existence of glycosuria.

Hypoglycemia

A blood sugar lower than normal, even to the point of inducing reactions, except just preceding and during labor, apparently is not harmful either to mother or fetus. In 14 patients with hypoglycemic manifestations, some reaching coma, anywhere from the second month of pregnancy to just before delivery, living babies were born in every instance (Herrick and Tillman[3]). Excessive doses of insulin just prior to

labor may result in hypoglycemia not only in the mother but also in the infant. This question will be discussed in a subsequent section.

Effect of Diabetes on the Pregnant Woman

Incidence of diabetes in pregnancy

The incidence of diabetes in pregnancy is not very great. This may be gathered from the statistics of the Municipal Hospitals in Greater New York which reveal that during the first six months of 1940 in a total of 8,598 pregnancies, there were 18 diabetic mothers, that is, 2.1 per thousand. For New York City the number of diabetic mothers is still lower, as shown by the reports of births and stillbirths to the Department of Health of New York City for 1939. During that year there were 83 diabetic mothers in 104,707 pregnancies, that is, 0.8 per thousand. The statistics on diabetes pregnancies from any one clinic are not conclusive, both because the reported cases are relatively few, and, furthermore, since the mode of dietetic management and insulin administration changes from time to time and any extensive series of diabetes pregnancies must be spread over a long period and the cases must thus be subject to considerable variation in treatment.

Infections of the urinary tract

According to Baldwin and Root,[11] infections of the urinary tract are more frequent, more protracted and of more serious outcome in the diabetic patient than in the non-diabetic. Whether or not this statement holds true in diabetics that are perfectly managed, that is, free from glycosuria, or are treated with protamine zinc insulin, remains to be proved though there is a good deal of evidence that hyperglycemia, in itself, does not favor the occurrence of infections. Hyperglycemia without glycosuria does not entail malnutrition of the tissues (protein destruction), dehydration (loss of sodium) or ketosis (incomplete oxidation of fatty acids). Consequently, bodily resistance is not diminished under those circumstances. It is possible that when protamine zinc insulin is used the same effects may be produced in spite of an existing glycosuria, though this observation of Tolstoi and Weber[10] must be verified.

Infections of the urinary tract which cause cystitis, pyelitis or pyelonephritis may bring about the toxemias of pregnancy which, because of the urinary tract involvement, would be of the hypertensive or vas-

cular type that Herrick and Tillman[3] claim is the most common form of toxemia of pregnancy in a diabetic.

Vitamin B_1 deficiency

Wilder[4] lays considerable stress on the fact that requirements for vitamin B_1 are increased from three to five times in normal pregnancy, and when diabetes exists, there is still further need of B_1 above the usual normal necessity. Some of the toxemias of pregnancy, the hyperemesis of pregnancy, and the fetal oversize, have all been blamed on a relative deficiency of vitamin B_1. Wilder reports one case in which glycosuria, albuminuria, hemorrhagic retinitis with edema of the optic disc, subjective disturbance of vision, and mental cloudiness, were corrected by intensive administration of vitamin B_1, and he notes that similar results have been obtained in many other cases.

Hormonal therapy

Hormonal therapy, designed to correct a rising blood prolan as carried out by Priscilla White[12] at the Deaconess Hospital in Boston, is, as I understand it, intended to check fetal mortality, whereas maternal risks are satisfactorily controlled by insulin and diet. This phase of the problem will therefore be considered in discussing the "Effect of diabetes upon the fetus."

Cesarean section

Cesarean section, carried out as a routine measure, has been advocated to insure a viable fetus. This subject will be discussed under the heading of "Effect of diabetes upon the fetus." However, the fact must not be lost sight of that cesarean section, regardless of diabetes, is much more dangerous to the mother than pelvic delivery and on that account deserves careful consideration before it is undertaken (Hurwitz and Irving[6]).

Effect of Diabetes Upon the Fetus and the Newborn Infant

Age of mother

The age of the mother is an important factor in infant mortality. This may be noted from Table II, in which it is shown that the infant mortality increases distinctly after age 30. The age of diabetic mothers with stillbirths is higher than the age of non-diabetic mothers with still-

TABLE II

Age of Mother	*Late Fetal and Neonatal Mortality*
Under 20	25.1 per 1000 total births
20 — 24	24.4 "
25 — 29	26.7 "
30 — 34	31.3 "
35 — 39	40.8 "
40 and over	61.5 "
For all mothers	29.6

Late fetal and neonatal mortality (full term births). Statistics from upstate New York—1936. *Age of mother an important factor in infant mortality.*

Ages of diabetic mothers with stillbirths considerably higher than those of non-diabetic mothers with stillbirths. Diabetic mothers 50 per cent are 35 years or older; non-diabetic mothers 23 per cent are 35 years or older. *Age of diabetic mothers with stillbirths greater than age of non-diabetic mothers with stillbirths.*

births. (Diabetic mothers 50 per cent are 35 years or older; non-diabetic mothers 23 per cent are 35 years or older). Consequently, it may be concluded that the older age of the mother is a factor in the greater tendency to late fetal mortality which is characteristic of diabetes.

Control of diabetes

The effects of poorly controlled diabetes and the significance of acidosis, hyper- and hypoglycemia have been discussed in the section on the "Effect of pregnancy on carbohydrate metabolism." It suffices at this point to stress the dangers of acidosis both to the fetus and the mother. Hurwitz and Irving[6] claim from their experience as well as from a study of the literature, that the most frequent cause of fetal death is neglect of the diabetes, with resultant acidosis. Maceration of the fetus is regarded as the complication of an uncontrolled diabetes (Potter and Adair[13]).

Overweight of the fetus

Fetal overweight has always been considered as a major hazard in diabetes pregnancies. The opinion appears to be growing that it occurs only when the diabetes of the mother has not been properly regulated (Potter and Adair[13]). Herrick and Tillman,[3] who stress the importance of control of diabetes throughout the entire pregnancy, state that among

the viable births the child of a diabetic mother is as likely to be underweight as overweight. Wilder[4] claims that he has not encountered large babies, possibly because in earlier cases, low carbohydrate diets were used, and recently, because the child had been delivered by cesarean section between the 36th and 37th week. Another possible explanation that Wilder puts forward has been his insistence on a diet richly supplied with vitamins and calcium, since it is not improbable that a relative lack of vitamin B_1 is responsible for an oversize fetus.

Overweight is due to an extensive accumulation of fat and not to skeletal changes.

It has been suggested that disturbances in pituitary activity, supposed to occur in diabetes, are responsible for the overweight.

The significance of all these claims and statements is not perfectly clear but one cannot help gaining the impression in reading from the various reports that as Potter and Adair put it: "If the patient's urine has been kept relatively sugar-free by diet and insulin, and acidosis has not occurred, a live-born infant within normal limits of size, will probably be delivered naturally."

Hormonal imbalance

Priscilla White and her co-workers for a long time have been furnishing evidence that accidents commonly seen in diabetes pregnancies are not due to imperfectly controlled diabetes but to an abnormal hormone balance. White and Hunt[12] in a recent publication summarize their point of view and their results as follows: "Our present conception of the mechanism of the accidents in diabetic pregnancies has been the outcome, first, of our realization that adequate dietary control of diabetes and insulin therapy did not lower the fetal mortality rate and, second, our correlation of the behavior of diabetic pregnancies in relation to the balance of pregnancy hormones—chorionic gonadotropin, estrogen and progesterone. We believe (1) that an abnormal rise of chorionic gonadotropin after the twentieth week to a level of 200 rat units per hundred cubic centimeters of blood predicts in the diabetic premature delivery, stillbirth and neonatal deaths, (2) that these accidents are caused by a failure of production or of metabolism of estrogen and progesterone and (3) that they are prevented by continuous substitutional estrogen and progesterone therapy in replacement doses."

Cesarean section

There are two schools of thought:—those who, like Wilder,[4] believe in early cesarean section in every diabetes pregnancy, and those who believe as do Herrick and Tillman[3] that cesarean section should be reserved for those cases in which there is a supporting obstetric indication. According to others there are special indications for cesarean section such as, the hormonal imbalance as sponsored by Priscilla White, or the excessive size of the fetus. In general, the trend seems to be toward a conservative attitude and the results reported by various authors when the diabetes has been controlled from the start, showed figures which are decidedly encouraging and comparable to those offered by the advocates of frequent recourse to cesarean section.

Hypoglycemia of the newborn

Wilder[4] claims that the usual cause of neonatal deaths is hypoglycemia as evidenced by the occurrence of convulsions and that this can be controlled by glucose injections. On the other hand, there are many (Miller and Ross,[14] Sisson,[15] and others[16, 17]) who are unable to confirm this finding.

In Sisson's [15] series of 65 infants born of diabetic mothers, a high blood sugar was the rule and hypoglycemia was a rare complication. A low blood sugar when it did occur was ascribed to insulin given to the mother just before delivery. The restriction of insulin to the minimum necessary for control of the diabetes just prior to delivery would therefore be clearly indicated. Consequently, the routine procedure of glucose injections directly after birth is useless and should not be carried out unless the actual blood sugar determination shows a hypoglycemia.

Hypoglycemia in the mother does not necessarily indicate that the infant will suffer on this account. Herrick and Tillman[3] note that in two patients with hypoglycemia while in labor, the fetal blood taken at the same time showed an extremely low level of sugar. Clinically, however, these infants behaved normally and gave no evidence of hypoglycemia.

Asphyxia of the infant

Asphyxia has been stressed as a frequent cause of neonatal death. Sisson[15] states that there seems to be a rather typical symptom complex. It usually occurs in the first 12 hours of life and is associated with fre-

quent and labored respirations. Physical examination shows unexpanded lungs. All reflexes are suppressed but muscular contractions of the face and extremities are common. The condition suggests an intrauterine disturbance with involvement of the respiratory center. In many instances the precipitating cause has seemed to be the insufflation of amniotic sac contents. This occurred most frequently with infants delivered before the eighth month. Wilder[4] describes the treatment of this condition as follows: "Following the delivery of the child, efforts are directed immediately to prevent hypoglycemia and to combat asphyxia. Care is taken to be certain that the pharynx and trachea are free of mucus and amniotic fluid, by keeping the head dependent and, if necessary, by aspirating with a tracheal catheter. Occasionally inhalation of carbon dioxide and oxygen is needed to establish respiration. When the baby is breathing it is placed in a Hess incubator equipped with a cover and connected with an oxygen tank. Flow of oxygen is regulated in order to maintain an oxygen concentration of 40 to 50 per cent for the first few hours. The concentration of oxygen in the incubator gradually is diminished and when the color of the infant remains normal in the ordinary atmosphere, administration of oxygen is discontinued."

Summary and Conclusions

Pregnancy accentuates an existing diabetes.

Pregnancy favors the development of diabetes in later years.

The older age of diabetic mothers is an unavoidable predisposing factor to stillbirths.

Large amounts of Vitamin B_1 are required during pregnancy and particularly when diabetes exists. According to Wilder many of the complications of diabetes pregnancies may be set aside by suitable doses of B_1.

The impression is growing that asphyxia of the infants of diabetic mothers is a frequent cause of neonatal death.

The opinion is expressed with increasing frequency that routine cesarean section is unnecessary in diabetes pregnancies and that equally good results are obtained when cesarean section is performed only when there is an obstetric complication that would be regarded as an indication for cesarean section in non-diabetes pregnancies.

It is possible and would appear to be probable that regulation of the diabetes (meaning adequate deposit of glycogen in the tissues, ample

oxidation of glucose and freedom from acidosis) from the very beginning to the termination of pregnancy in a diabetic woman will do away with all the complications of pregnancy to which mother and fetus are liable. This includes oversize, maceration and other fetal hazards. The diabetes should not only be well controlled from day to day but care should be taken that the body's carbohydrate metabolism is proceeding along normal paths and providing proper utilization of glucose every hour of the day and night. This is stressed because with protamine zinc insulin we now have an agent which furnishes perfect adjustment of glucose assimilation continuously for more than 24 hours and has distinct advantages over the first, unmodified insulin which acted for only 4 hours after each injection and failed to prevent a resumption of the diabetic state after its period of influence had ceased. It would seem possible that all the problems of pregnancies in diabetic subjects may be solved by complete control of the carbohydrate metabolism from the very beginning of pregnancy to the termination of labor, and for the accomplishment of this end protamine zinc insulin should prove to be of inestimable help.

Sudden and marked variations in the severity of the diabetes may occur in the course of pregnancy, especially during the second and third trimesters. Such changes may call for either more or less insulin. If these demands are not met, serious consequences are in store for both mother and child. Therefore, during the second and third trimesters the diabetes should be regulated every 7 to 10 days.

During labor the most meticulous care should be taken to check acidosis and to prevent hypoglycemia in the mother. All authors are agreed on the point that acidosis is a very serious complication and because of its fulminating progress must be regarded as an emergency. The occurrence of the dangerous hypoglycemia in the newborn apparently can be prevented by keeping the insulin administration to the prospective mother within reasonable limits, as governed by blood sugar determinations.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

JANUARY 8—*The New York Academy of Medicine. Annual Meeting.* Executive session—a] Reading of the Minutes; b] Amendment to By-Laws; c] Presentation of diplomas. ¶ Presentation of annual reports (to be read by title): The Council, The Trustees, The Treasurer, Committees. ¶ Papers of the evening, *Program under the joint sponsorship of The New York Academy of Medicine and its Section of Surgery and The New York Surgical Society*—War Wounds—a] Determining factors in the end-results following war wounds and compound fractures, H. Winnett Orr, Chief Surgeon, Nebraska Orthopedic Hospital; b] The treatment of head injuries, James C. White, Assistant Professor of Surgery, Harvard Medical School. ¶ Report of election of fellows.

JANUARY 15—*The Harvey Society in affiliation with The New York Academy of Medicine.* The fourth Harvey lecture, "Intermediary Metabolism in Diabetes Mellitus," William C. Stadie, Professor of Research Medicine, University of Pennsylvania.

SECTION MEETINGS

JANUARY 6—*Dermatology and Syphilology.* Presentation of cases—a] Presbyterian Hospital; b] Vanderbilt Clinic. ¶ Discussion. ¶ Executive session.

JANUARY 6—*Combined Meeting Section of Neurology and Psychiatry and the New York Neurological Society.*—a] Reading of the minutes; b] Case presentation. Neurosis of seventy-years' standing, C. P. Oberndorf, Arnold Eisendorfer. ¶ Papers of the evening—a] Spastic and flaccid hemiplegia of cerebral origin, Ben H. Balser; Discussion, Tracy J. Putnam, Margaret A. Kennard; b] Visualization of the brain and spinal cord with diiodotyrosine gelatine contrast media including later observations, Harold H. Lefft, J. Arthur MacLean; Discussion, Tracy J. Putnam, Leo M. Davidoff.

JANUARY 8—*Combined Meeting Section of Historical and Cultural Medicine and the Section of Pediatrics.* ¶ Papers of the evening—a] The throat distemper of 1735-1740, Ernest Caulfield (by invitation); b] The evolution of our present knowledge of hypersensitiveness, Bret Ratner; Discussion, Ulrich Friedemann (by invitation), Bela Schick.

JANUARY 19—*Ophthalmology.* ¶ Instruction hour 7:00 to 8:00 o'clock. Visual pathways—A clinical review, Ferdinand Koch (by invitation). ¶ Exhibit—Exophthalmos, A. D. Ruedemann, Cleveland (by invitation). ¶ Executive session. Reading of the minutes. ¶ Presentation of cases—a] A case of molluscum contagiosum of the lid margin with pannus, Clement McCulloch (by invitation); b] A case of tuberous sclerosis, Murray Last. ¶ Papers of the evening—a] Heparin treatment of thrombosis of the central retinal vein, Marion Cuthbert (by invitation); b] The clinical and surgical aspects of pituitary tumors, Leo M. Davidoff; c] The roentgenological aspects of pituitary tumors, Cornelius G. Dyke; Discussion, Foster Kennedy.

JANUARY 20—*Joint Scientific Session Section of Medicine and the New York Heart Association, Heart Committee of the New York Tuberculosis and Health Association.* Annual report of the New York Heart Association, Ernst P. Boas. ¶ Papers of the evening—a] Experimental and clinical studies in the use of anti-coagulants in cardiovascular disease with special reference to heparin and dicoumarin, Andrew G. Prandoni (by invitation), Department of Internal

Medicine, New York Post-Graduate Medical School & Hospital, Columbia University; Discussion, Irving S. Wright; b] Some chemical changes in the myocardium accompanying heart failure, Victor C. Myers (by invitation), Professor of Biochemistry, Western Reserve University, Cleveland, Ohio; Discussion, Maurice Bruger (by invitation).

JANUARY 21—*Genito-Urinary Surgery.* Reading of the minutes. ¶ Papers of the evening—a] Studies on the etiology of Hunner ulcer, Edward Cathcart, Detroit (by invitation); b] Bladder complications following operations for advanced rectal carcinoma—a new operative device, Benjamin Barringer; c] The treatment of neurogenic urinary incontinence with trasentin. Studies in bladder function (lantern slides), Irving Simons; Discussion, J. Sturdivant Read.

JANUARY 21—*Otolaryngology.* Reading of the minutes. ¶ Presentation of cases—a] Lipoid proteosis, Marion B. Sulzberger; Discussion, Julius F. Neuberger (by invitation). ¶ Papers of the evening—a] Histamine in the treatment of nasal allergy, Laurence Farmer; Discussion, Arthur J. Cracovaner; b] Experiences in the treatment of Ménière's syndrome, Miles Atkinson (by invitation); Discussion, Foster Kennedy. ¶ General discussion. ¶ Executive session.

JANUARY—*Orthopedic Surgery.* No meeting of the Section was held in January because of the annual meeting of the American Academy of Orthopædic Surgeons in Atlantic City, January 11-15.

JANUARY 27—*Obstetrics and Gynecology.* Program presented by the Woman's Hospital. ¶ Executive session, reading of the minutes. ¶ Papers of the evening—a] Uterine prolapse, its management and surgical treatment, Ralph A. Hurd; b] Carcinoma of the corpus uteri, Diagnosis and treatment, George Gray Ward; c] Caesarean section, Advantages and disadvantages of the various surgical techniques, James P. Marr; d] Maternal mortality, A consideration of common errors in the conduct of labor and delivery, Ralph L. Barrett, Chairman Special Committee on Maternal Welfare, New York County Medical Society. ¶ General discussion.

AFFILIATED SOCIETIES

JANUARY 22—*New York Pathological Society in affiliation with The New York Academy of Medicine.* ¶ Papers of the evening — Iso-immunization and the pathogenesis of erythroblastosis fetalis: a] The pathogenesis of erythroblastosis fetalis, Philip Levine (by invitation); b] The pathological aspects of erythroblastosis fetalis, S. H. Polayes; c] The clinical and hematological aspects of erythroblastosis fetalis, Peter Vogel (by invitation); d] Iso-immunization and the prevention of intra-group transfusion accidents, E. M. Katzin (by invitation). ¶ Executive session, election of officers.

JANUARY—*New York Roentgen Society.* The regular monthly meeting of the Society was omitted in January, because of the Annual Mid-winter Eastern Conference of Radiologists, which was held January 23 and 24 at the Hotel Biltmore, New York.

DEATHS OF FELLOWS

FOSTER, ALLYN KING, JR.: 136 East 57 Street, New York City; born in Cornwall, Connecticut, March 8, 1905; died in New York City, January 17, 1942; graduated in medicine from Rush Medical College, University of Chicago, in 1929; elected a Fellow of the Academy January 7, 1937.

Dr. Foster had served his internship at St. Luke's Hospital and was junior assistant surgeon to the Post-Graduate Hospital, assistant surgeon to the Downtown Hospital, assistant surgeon to the O.P.D. at Post-Graduate Hospital and clinical assistant surgeon to the O.P.D. of the Lincoln Hospital. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

FURNISS, HENRY DAWSON: 54 East 62 Street, New York City; born in Selma, Alabama, March 25, 1878; died in New York City, January 25, 1942; graduated in medicine from the Medical Department of the University of Virginia in 1899; elected a Fellow of the Academy March 7, 1907.

Dr. Furniss was professor of obstetrics and gynecology at the New York Medical College and attending obstetrician and gynecologist to the Flower and Fifth Avenue Hospitals; visiting surgeon to the Metropolitan Hospital; consulting gynecologist to the New York Post-Graduate Hospital, Broad Street Hospital, New Rochelle Hospital, St. Luke's Hospital at Newburgh, Holy Name Hospital at Teaneck, Hackensack Hospital of New Jersey, All Soul's Memorial Hospital at Morristown, and consulting cystoscopist to the New York Infirmary for Women and Children. From 1917 to 1927, Dr. Furniss was professor of gynecology at the New York Post-Graduate Medical School, having joined that faculty in 1904 as instructor of gynecology.

Dr. Furniss was a diplomate of the American Board of Urology, a diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, a member of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons, the Southern Surgical Society, the American Urological Association, and the State and County Medical Societies.

GOODFRIEND, NATHAN: 44 West 77 Street, New York City; born in Galsech, Austria-Hungary, June 18, 1880; died in New York City, January 17, 1942; graduated in medicine from the College of Physicians and Surgeons in 1902; elected a Fellow of the Academy April 3, 1913.

Dr. Goodfriend was attending ophthalmologist to the Bronx Hospital and secretary of its medical board; and assistant surgeon to the Manhattan Eye, Ear and Throat Hospital. He was a Fellow of the American Medical Association, a Fellow of the American College of Surgeons and a member of the State and County Medical Societies.

LOUGHRAN, ROBERT LIVINGSTON: Sharon, Connecticut; born in Kingston, New York, March 28, 1873; died in Sharon, January 27, 1942; received the degree of A.B. from Princeton University in 1895; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1899; elected a Fellow of the Academy May 18, 1905.

Dr. Loughran was at one time professor of otology and attending otologist to the New York Post-Graduate Medical School and Hospital. He was a diplomate of the American Board of Otolaryngology, a Fellow of the American College of Surgeons, a member of the American Laryngological, Rhinological and Otological Society and its secretary from 1924 to 1936, and a member of the American Medical Association and the State and County Medical Societies.

In the first world war, Dr. Loughran held the rank of Major in the Army Medical Corps. He served as superintendent of the Ancon Hospital and as Chief Public Health Officer of the Panama Canal Zone from 1917 to 1919.

TAYLOR, ALFRED SIMPSON: 116 East 68 Street, New York City; born in Manchester, Connecticut, January 17, 1868; died in New York City, January 16, 1942; received from Brown University the degrees of Ph.B. in 1891 and A.M. in 1892; graduated in medicine from the College of Physicians and Surgeons in 1895; elected a Fellow of the Academy February 4, 1904.

Dr. Taylor was professor of clinical surgery of the neurological department at Cornell University Medical College from 1910 to 1930. He was consulting surgeon to the Memorial, Fordham and New York Hospitals; and consulting neurosurgeon to the New York Neurological Institute and St. Luke's, General Memorial and Tarrytown Hospitals. He was a Fellow of the American Medical Association and the American College of Surgeons; and a member of the American Surgical Society, the Society of Neurological Surgeons, the American Neurological Association and the County and State Medical Societies.

Dr. Taylor contributed many papers in the field of general and neurosurgery and developed a method for the reduction of dislocations of the spine.

WALDIE, THOMAS EDWARD, 1215 Madison Avenue, New York City; born in Brooklyn, November 20, 1884; died in New York City, September 18, 1941; graduated in medicine from Cornell University Medical School in 1907; elected a Fellow of the Academy, January 6, 1927.

Dr. Waldie was a member of the State and County Medical Societies, and the American Medical Association. He was Pediatrician to St. Vincent's, St. Clares, Willard Parker and the New York Foundling Hospitals, and Director of the Department of Pediatrics of the Misericordia Hospital.

WOLFF, JULIUS: 1112 Park Avenue, New York City; born in New York City, December 3, 1869; died in New York City, January 26, 1942; received the degree of A.B. from Harvard University in 1890; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1893; elected a Fellow of the Academy May 4, 1899.

Dr. Wolff was ophthalmologist to Randall's Island Hospital, 1899-1905; and assistant ophthalmic surgeon to Bellevue Hospital, 1927-32. In 1907 he became associated with The Mount Sinai Hospital as assistant adjunct attending surgeon; from 1923 to 1932 he was attending ophthalmic surgeon and head of the department of ophthalmology; and from 1932 until the time of his death, he was consulting ophthalmologist to that institution. He was a diplomate of the American Board of Ophthalmology, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.